Request — Noble Jarrell

Access DB# 150678

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Sabiha Qazi Examiner #: 74141 Date: 4/13/05

Art Unit: 1616 Phone Number 30 20622 Serial Number: 10/781,120

Mail Box and Bldg/Room Location: 4C70, Rm, 4445 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of invention: 1,3 20,20 diethyl Vitamin D_3 analogs

Inventors (please provide full names): Percy Manchand

Earliest Priority Filing Date: 2/18/04

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Cls 31 — 39 + 43

Please search for the compds of formula 1) in cl 1

Please see attached Sheet

Thank you

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Noble	NA Sequence (#)	STN ✓ 586
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#) 1	Questel/Orbit
Date Searcher Picked Up:	Bibliographic ✓	Dr.Link
Date Completed: 4/29/05	Litigation	Lexis/Nexis
Searcher Prep & Review Time: 5	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time: 34	Other	Other (specify)

PTO-1590 (8-01)

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=> d his full

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L1            1 SEA ABB=ON  PLU=ON  (US20040167105 OR US20030083319 OR
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     FILE 'HCAPLUS' ENTERED AT 07:55:58 ON 29 APR 2005
L2            TRA L1 1- RN :       38 TERMS

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L3           38 SEA ABB=ON  PLU=ON  L2

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FILE LAST UPDATED: 28 Apr 2005  (20050428/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L1   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:194114  HCAPLUS
DN   130:223485
ED   Entered STN:  25 Mar 1999
TI   Preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for
     pharmaceutical use
IN   Manchand, Percy Sarwood; Uskokovic, Milan Radoje
PA   F. Hoffmann-La Roche A.-G., Switz.
SO   PCT Int. Appl., 60 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  C07C401-00
     ICS  A61K031-59
CC   32-7 (Steroids)
     Section cross-reference(s): 1, 2, 63
FAN. CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
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PI   WO 9912894           A1     19990318    WO 1998-EP5571           19980902 <--
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             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
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NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
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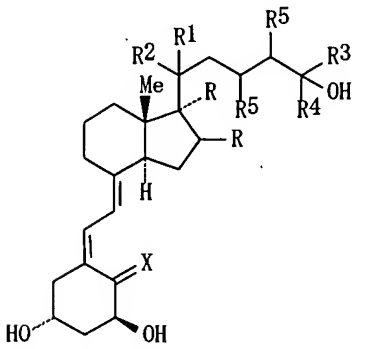
US 6492353	B1	20021210	US 1998-148018	19980903	<--
US 2003083319	A1	20030501	US 2002-206430	20020725	<--
US 2004167105	A1	20040826	US 2004-781120	20040218	<--
PRAI US 1997-58132P	P	19970908	<--		
WO 1998-EP5571	W	19980902			
US 1998-148018	A1	19980903			
US 2002-206430	A1	20020725			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9912894	ICM	C07C401-00	
	ICS	A61K031-59	
WO 9912894	ECLA	A61K031/59P; C07C401/00	<--
US 6492353	NCL	514/167.000; 552/653.000	
	ECLA	A61K031/593	<--
US 2003083319	NCL	514/167.000; 552/653.000	
	ECLA	A61K031/59P; A61K031/593; C07C401/00	<--
US 2004167105	NCL	514/167.000; 552/653.000	
	ECLA	A61K031/59P; A61K031/593; C07C401/00	<--

OS MARPAT 130:223485

GI



I

AB 1,3-Dihydroxy-20,20-dialkyl-vitamin D3 analogs I [R = H; RR = bond; R1, R2, R3, R4 = H, alkyl, fluoroalkyl; R1R2, R3R4 = cycloalkyl, cyclofluoroalkyl; R5 = H; R5R5 = bond, double bond; X = H2, CH2] were prepared and formulated for pharmaceutical use for treatment of osteoporosis, secondary hyperparathyroidism, cancer and autoimmune diseases. Thus, 23-yne-cholecalciferol I [R = H, R1R2 = CH2CH2, R3 = R4 = Me, R5R5 = double bond, X = CH2] was prepared starting from (1,1-dimethylethyl)dimethyl[[(1R,3aR,4S,7aR)-octahydro-7a-methyl-1-(1-methylethenyl)-1H-inden-4-yl]oxy]silane and [(2Z)-2-[(3S,5R)-3,5-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenecyclohexylidene]ethyl]diphenyl phosphine oxide. The prepared compds. were tested for bone anabolism in the rat, antiproliferative activity against MCF-7 breast cancer cells, and effect on secondary hyperparathyroidism.

ST vitamin D3 analog prepn bone anabolism; antiproliferative agent vitamin D3

analog prepn; antitumor agent vitamin D3 analog prepn; osteoporosis treatment vitamin D3 analog prepn; hyperparathyroidism treatment vitamin D3 analog prepn; autoimmune treatment vitamin D3 analog prepn; cholecalciferol analog prepn bone anabolism

IT Antitumor agents
(mammary gland; preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT Mammary gland
(neoplasm, inhibitors; preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT Antitumor agents
Autoimmune disease
Cytotoxic agents
(preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT Proliferation inhibition
(proliferation inhibitors; preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT Hyperparathyroidism
(secondary; preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT Osteoporosis
(therapeutic agents; preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT 221046-03-3P 221046-04-4P 221046-05-5P 221046-06-6P 221046-07-7P 221046-09-9P 221046-10-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT 67-64-1, Acetone, reactions 684-16-2, Hexafluoroacetone 25411-73-8, Diethyldiazomethyl phosphonate 81522-68-1 139356-39-1 215257-72-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

IT 199730-85-3P 221046-11-3P 221046-12-4P 221046-13-5P 221046-15-7P 221046-16-8P 221046-17-9P 221046-18-0P 221046-19-1P 221046-20-4P 221046-21-5P 221046-22-6P 221046-24-8P 221046-25-9P 221046-26-0P 221046-27-1P 221046-28-2P 221046-29-3P 221046-30-6P 221046-31-7P 221046-32-8P 221046-33-9P 221046-34-0P 221046-35-1P 221046-36-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 1,3-dihydroxy-20,20-dialkyl-vitamin D3 analogs for pharmaceutical use in the treatment of osteoporosis, secondary hyperparathyroidism, cancer, and autoimmune diseases)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) F Hoffmann-La Roche Ag; US 5428029 A HCAPLUS
(2) F Hoffmann-La Roche Ag; US 5451574 A HCAPLUS
(3) F Hoffmann-La Roche Ag; EP 0580968 A 1994 HCAPLUS
(4) F Hoffmann-La Roche Ag; EP 0654467 A 1995 HCAPLUS
(5) F Hoffmann-La Roche & Co Ag; EP 0326875 A 1989 HCAPLUS
(6) Laboratoire Theramex Sa; WO 9501960 A 1995 HCAPLUS
(7) Leo Pharmaceutical Products Ltd; WO 8910351 A 1989 HCAPLUS
(8) Schering Ag; US 5585368 A HCAPLUS
(9) Schering Ag; WO 9312081 A 1993 HCAPLUS
(10) Schering Ag; WO 9400428 A 1994 HCAPLUS

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FILE LAST UPDATED: 27 APR 2005 <20050427/UP>
MOST RECENT DERWENT UPDATE: 200527 <200527/DW>
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L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-229204 [19] WPIX
DNC C1999-067405
TI Treatment of osteoporosis, secondary hyperparathyroidism or cancer - using new or known 20,20-di alkyl-1,3-di hydroxy-vitamin-D3 analogs.
DC B05
IN MANCHAND, P S; USKOKOVIC, M R
PA (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE INC; (MANC-I) MANCHAND P S; (USKO-I) USKOKOVIC M R; (SYNT) SYNTEX LLC
CYC 83
PI WO 9912894 A1 19990318 (199919)* EN 59 C07C401-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
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EP 1015423 A1 20000705 (200035) EN C07C401-00
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EP 1015423 B1 20030502 (200330) EN C07C401-00
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 2003083319 A1 20030501 (200331) C07C401-00 <--
DE 69814109 E 20030605 (200345) C07C401-00
ES 2196614 T3 20031216 (200413) C07C401-00
US 2004167105 A1 20040826 (200457) A61K031-59 <--
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2002-206430 20020725, US 2004-781120 20040218
FDT AU 9910229 A Based on WO 9912894; EP 1015423 A1 Based on WO 9912894; JP 2001515881 W Based on WO 9912894; EP 1015423 B1 Based on WO 9912894; DE 69814109 E Based on EP 1015423, Based on WO 9912894; ES 2196614 T3 Based on EP 1015423; US 2004167105 A1 Cont of US 6492353
PRAI **US 1997-58132P 19970908**; US 1998-148018 19980903; US 2002-206430 20020725; US 2004-781120 20040218
IC ICM A61K031-59; C07C401-00; C07C401-01
ICS A61P019-10; A61P035-00; A61P043-00
AB WO 9912894 A UPAB: 19990525
NOVELTY - Medicaments for treatment of osteoporosis or secondary hyperparathyroidism, containing a 20,20-dialkyl-1,3-dihydroxy-vitamin D3 analog (I). Some compounds (I) are new. DETAILED DESCRIPTION - A medicament for treating osteoporosis or secondary hyperparathyroidism contains a 20,20-dialkyl-1,3-dihydroxy-vitamin D3 analog of formula (I) or its prodrug. X = H or =CH2; A = single or double bond; B = single, double or triple bond; R1-R4 = 1-4C alkyl or 1-4C fluoroalkyl; or CR1R2 = =CH2, 3-6C cycloalkylidene or 3-6C fluorocycloalkylidene; or CR3R4 = 3-9C cycloalkylidene or 3-9C fluorocycloalkylidene. Compounds (I) and their prodrugs are new, provided that: (i) if R1,R2 = 1-4C alkyl or CR1R2 = cyclopropyl or =CH2, R3,R4 = 1-4C alkyl or CF3 or CR3R4 = 3-6C cycloalkylidene and A = single bond, then B is not a trans double bond; (ii) if B = single bond, then CR1R2 = 3-6C cycloalkyl or 3-6C fluorocycloalkyl; and (iii) if R1-R4 = 1-4C alkyl, X = =CH2 and A = single bond, then B is not a double bond.

USE - (I) are bone anabolic agents and vitamin D3 receptor activity modulators. They are useful for prophylaxis and treatment of a variety of conditions involving loss of bone mass, including osteoporosis (e.g. of post-menopausal, senile or iatrogenic type, or associated with immunosuppressive drugs), osteopenia (e.g. due to cortico-steroid drugs), osteodystrophy (e.g. due to renal dialysis) and primary and secondary hyperparathyroidism. (I) are also useful in treating neoplastic diseases (e.g. leukemia, or breast, colon or prostate cancer); and immunosuppressive and autoimmune disorders (e.g. multiple sclerosis, systemic lupus erythematosus, diabetes, thyroiditis and allograft rejection). Use of the new compounds (I) for treating cancer is claimed.

ADVANTAGE - (I) can replete circulating vitamin D3 levels without causing hypercalcemic effects, hypercalcuria and nephrotoxicity, and thus have a better therapeutic index than prior art drugs such as calcitriol.

Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B03-G; B14-G02D; B14-H01; B14-N01; B14-N11

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     FILE 'REGISTRY' ENTERED AT 07:55:58 ON 29 APR 2005
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L7             STR L6
               D QUE L7
L8             3 SEA CSS SAM L7
               D SCA
L9            66 SEA CSS FUL L7
               SAV TEM QAZ120F0/A L9
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L16        21797 SEA ABB=ON  PLU=ON  (HOFFMAN# OR LA (1A) ROCHE OR LAROCHE OR
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L19           16 SEA ABB=ON  PLU=ON  L13 NOT L17
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L21           36 SEA ABB=ON  PLU=ON  L18 AND L20
L22           16 SEA ABB=ON  PLU=ON  L19 AND L20
               SEL AN L22 3-5
L23            3 SEA ABB=ON  PLU=ON  ("135:190779"/AN OR "137:261692"/AN OR
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                 "2003:273505"/AN) AND L22

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DICTIONARY FILE UPDATES: 27 APR 2005 HIGHEST RN 849400-77-7

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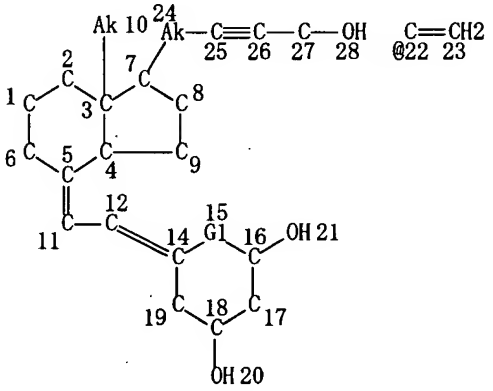
L7 STR



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CONNECT IS M1 RC AT 24
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
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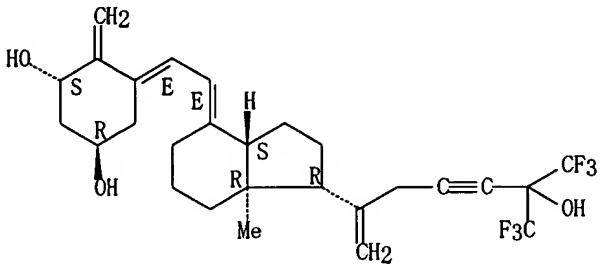
L10 15 SEA FILE=REGISTRY ABB=ON PLU=ON (119290-65-2/BI OR 121664-09-3/BI OR 121664-11-7/BI OR 144100-33-4/BI OR 162581-25-1/BI OR 163217-09-2/BI OR 163217-11-6/BI OR 163379-89-3/BI OR 205673-01-4/BI OR 248257-53-6/BI OR 386766-89-8/BI OR 387352-55-8/BI OR 387357-66-6/BI OR 762303-09-3/BI OR 807374-44-3/BI) AND L9

=> d ide l10 tot

L10 ANSWER 1 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **807374-44-3** REGISTRY
ED Entered STN: 03 Jan 2005
CN 9,10-Secocholesta-5,7,10(19),20-tetraen-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,5E,7Z)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H32 F6 03
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.
Double bond geometry as shown.

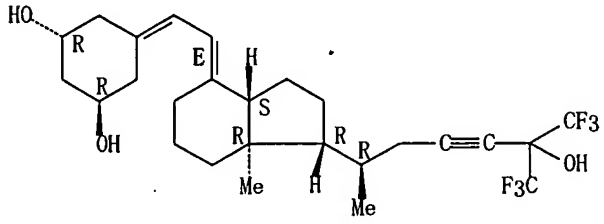


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 2 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **762303-09-3** REGISTRY
ED Entered STN: 14 Oct 2004
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,7E)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H34 F6 03
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.
Double bond geometry as shown.

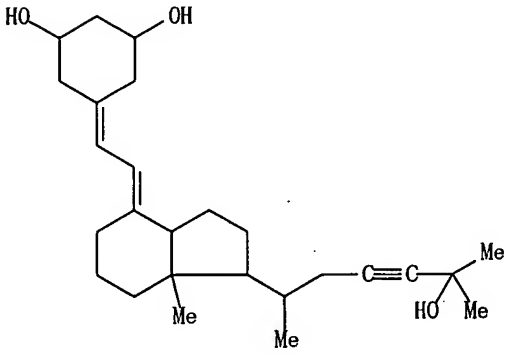


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 3 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **387357-66-6** REGISTRY

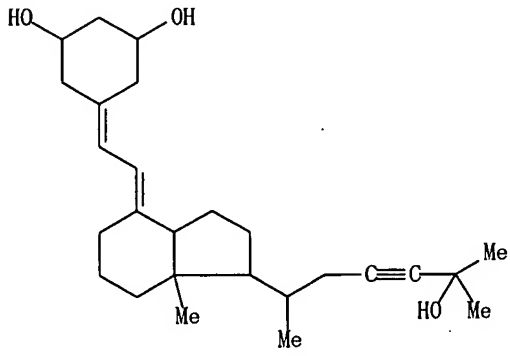
ED Entered STN: 28 Jan 2002
CN 19-Nor-9, 10-secocholesta-5, 7-dien-23-yne-1, 3, 25-triol, (1α, 3α, 5E, 7Z, 14β)- (9CI) (CA INDEX NAME)
MF C26 H40 O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 4 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **387352-55-8** REGISTRY
ED Entered STN: 28 Jan 2002
CN 19-Nor-9, 10-secocholesta-5, 7-dien-23-yne-1, 3, 25-triol, (1α, 3α, 5Z, 7E, 14β)- (9CI) (CA INDEX NAME)
MF C26 H40 O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

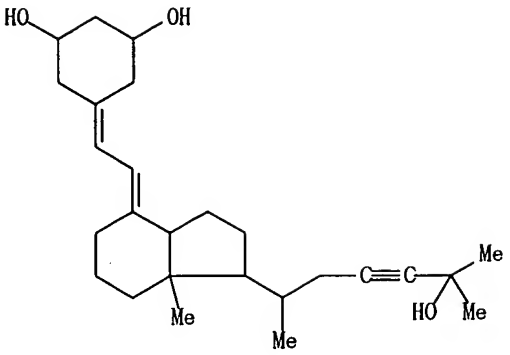


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 5 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **386766-89-8** REGISTRY
ED Entered STN: 25 Jan 2002
CN 19-Nor-9, 10-secocholesta-5, 7-dien-23-yne-1, 3, 25-triol, (1α, 3α, 5Z, 7Z, 14β)- (9CI) (CA INDEX NAME)
MF C26 H40 O3
SR CA
LC STN Files: CA, CAPLUS

Search done by Noble Jarrell

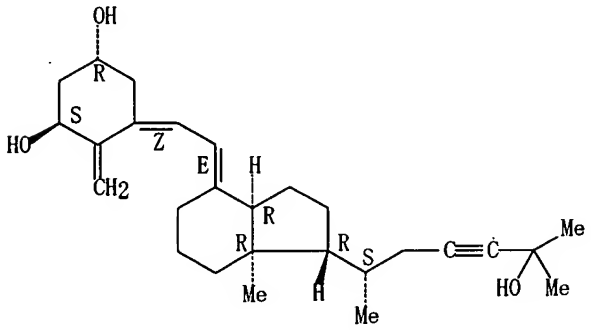


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 6 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **248257-53-6** REGISTRY
ED Entered STN: 22 Nov 1999
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E,14β,20S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H40 O3
SR CA

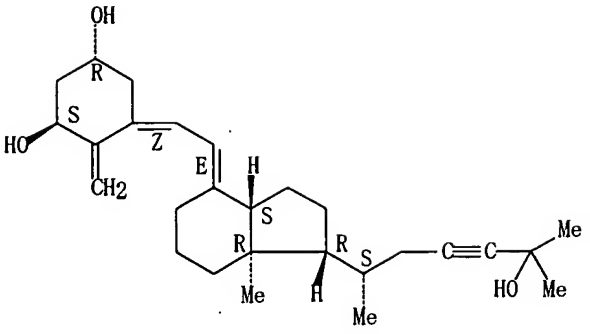
Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L10 ANSWER 7 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **205673-01-4** REGISTRY
ED Entered STN: 20 May 1998
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E,20S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H40 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

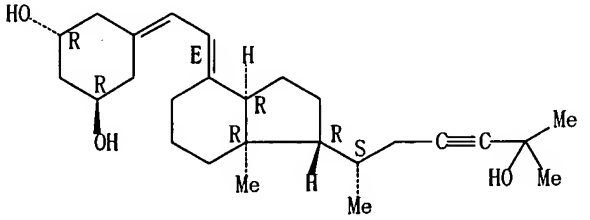


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 8 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **163379-89-3** REGISTRY
ED Entered STN: 31 May 1995
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN TX 527
FS STEREOSEARCH
MF C26 H40 O3
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

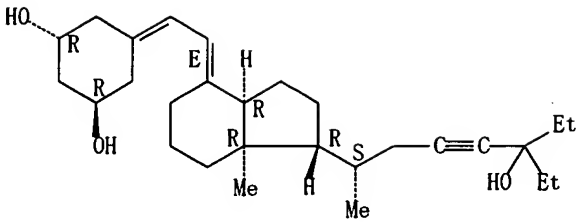


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 9 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **163217-11-6** REGISTRY
ED Entered STN: 24 May 1995
CN 1,3-Cyclohexanediol, 5-[[1-(5-ethyl-5-hydroxy-1-methyl-3-heptynyl)octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-, [1R-[1α(S*),3aα,4E(1R*,3R*),7aα]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H44 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

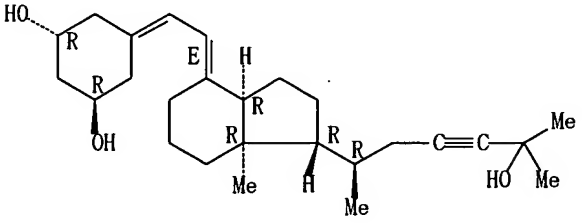


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 10 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **163217-09-2** REGISTRY
ED Entered STN: 24 May 1995
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,3-Cyclohexanediol, 5-[(2E)-[(1R,3aR,7aR)-octahydro-1-[(1R)-5-hydroxy-1,5-dimethyl-3-hexynyl]-7a-methyl-4H-inden-4-ylidene]ethylidene]-, (1R,3R)-
CN Inecalcitol
CN TX 522
FS STEREOSEARCH
MF C26 H40 O3
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CASREACT, TOXCENTER, USAN, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

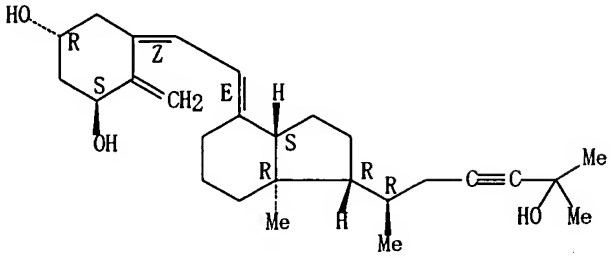
5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 11 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **162581-25-1** REGISTRY
ED Entered STN: 28 Apr 1995
CN Retinoic acid, mixt. with (1α,3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)-, mixt. contg. (9CI)
OTHER NAMES:
CN Ro 23-7498-retinoic acid mixt.
FS STEREOSEARCH
MF C27 H40 O3 . C20 H28 O2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

CM 1

CRN 119290-65-2
CMF C27 H40 O3

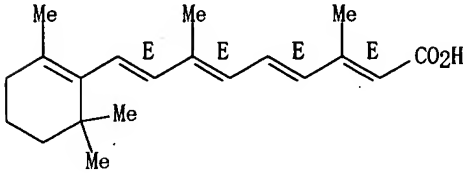
Absolute stereochemistry.
Double bond geometry as shown.



CM 2

CRN 302-79-4
CMF C20 H28 O2

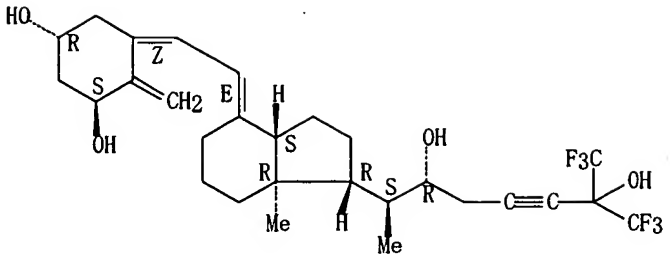
Double bond geometry as shown.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 12 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **144100-33-4** REGISTRY
ED Entered STN: 23 Oct 1992
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-7a-methyl-1-[(1S,2R)-7,7,7-trifluoro-2,6-dihydroxy-1-methyl-6-(trifluoromethyl)-4-heptynyl]-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,3-Cyclohexanediol, 3-methylene-4-[[octahydro-7a-methyl-1-[7,7,7-trifluoro-2,6-dihydroxy-1-methyl-6-(trifluoromethyl)-4-heptynyl]-4H-inden-4-ylidene]ethylidene]-, [1R-[1α(1S*,2R*),3aβ,4E(1R*,3S*,5Z),7a.alpha.]]-
FS STEREOSEARCH
MF C28 H36 F6 O4
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

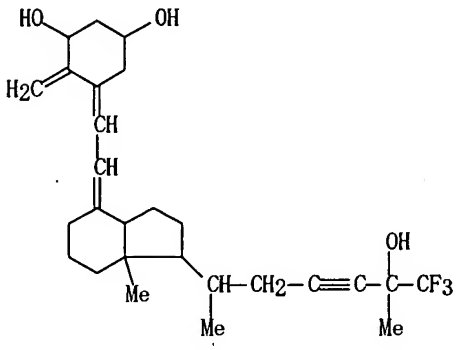
Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 13 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **121664-11-7** REGISTRY
ED Entered STN: 21 Jul 1989
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, 26,26,26-trifluoro-, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)
MF C27 H37 F3 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

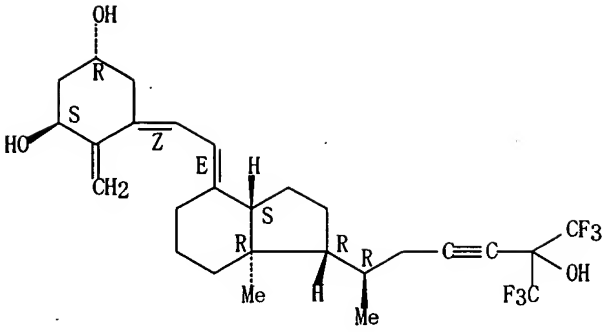


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 14 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **121664-09-3** REGISTRY
ED Entered STN: 21 Jul 1989
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H34 F6 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

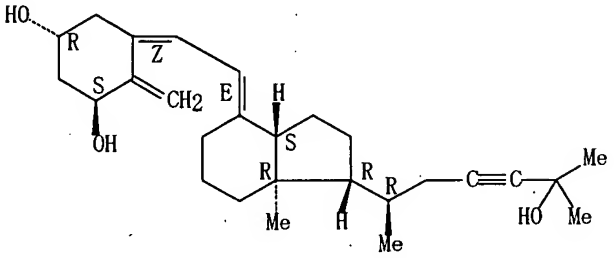


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 15 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN
RN **119290-65-2** REGISTRY
ED Entered STN: 24 Feb 1989
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Ro 23-7498
FS STEREOSEARCH
MF C27 H40 O3
CI COM
SR CA
LC STN Files: BIOTECHNO, CA, CAPLUS, DDFU, DRUGU, EMBASE, TOXCENTER, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

19 REFERENCES IN FILE CA (1907 TO DATE)
19 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> b hcap

FILE 'HCAPLUS' ENTERED AT 08:27:15 ON 29 APR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 29 Apr 2005 VOL 142 ISS 19
FILE LAST UPDATED: 28 Apr 2005 (20050428/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all fhitstr l17 tot

L17 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:113264 HCAPLUS
DN 135:28640
ED Entered STN: 15 Feb 2001
TI Highly active analogs of 1α,25-dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways
AU Uskokovic, M. R.; Norman, A. W.; **Manchand, P. S.**; Studzinski, G. P.; Campbell, M. J.; Koeffler, H. P.; Takeuchi, A.; Siu-Caldera, M.-L.; Rao, D. S.; Reddy, G. S.
CS **Hoffmann-La Roche** Inc., Nutley, NJ, 07110, USA
SO Steroids (2001), 66(3-5), 463-471
CODEN: STEDAM; ISSN: 0039-128X
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 2
AB The secosteroid hormone 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3] is metabolized in its target tissues through modifications of both the side chain and the A-ring. The C-24 oxidation pathway, the main side chain modification pathway is initiated by hydroxylation at C-24 of the side chain and leads to the formation of the end product, calcitroic acid. The C-23 and C-26 oxidation pathways, the minor side chain modification pathways are initiated by hydroxylations at C-23 and C-26 of the side chain and lead to the formation of the end product, calcitriol lactone. The C-3 epimerization pathway, the newly discovered A-ring modification pathway is initiated by epimerization of the hydroxyl group at C-3 of the A-ring to form 1α,25(OH)2-3-epi-D3. A rational design for the synthesis of potent analogs of 1α,25(OH)2D3 is developed based on the knowledge of the various metabolic pathways of 1α,25(OH)2D3. Structural modifications around the C-20 position, such as C-20 epimerization or introduction of the 16-double bond affect the configuration of the side chain. This results in the arrest of the C-24 hydroxylation initiated cascade of side chain modifications at the C-24 oxo stage, thus producing the stable C-24 oxo metabolites which are as active as their parent analogs. To prevent C-23 and C-24 hydroxylations, cis or trans double bonds, or a triple bond are incorporated in between C-23 and C-24. To prevent C-26 hydroxylation, the hydrogens on these carbons are replaced with fluorines. Furthermore, testing the metabolic fate of the various analogs with modifications of the A-ring, it was found that the rate of C-3 epimerization of 5,6-trans or 19-nor analogs is decreased to a significant extent. Assembly of all these protective structural modifications in single mols. has then produced the most active vitamin D3 analogs 1α,25(OH)2-16,23-E-diene-26,27-hexafluoro-19-nor-D3 (Ro 25-9022), 1α,25(OH)2-16,23-Z-diene-26,27-hexafluoro-19-nor-D3 (Ro 26-2198), and 1α,25(OH)2-16-ene-23-yne-26,27-hexafluoro-19-nor-D3 (Ro 25-6760), as indicated by their antiproliferative activities.
ST dihydroxyvitamin D3 analog biol activity structure
IT Antitumor agents
Structure-activity relationship
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)

IT Cell differentiation
(inducers; highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT 32222-06-3, Ro 21-5535 118694-43-2, Ro 23-7553 124409-58-1, Ro 24-2637 137102-93-3, Ro 24-5531 156208-06-9, Ro 25-6760 215714-85-5, Ro 25-7260
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT 343970-32-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT **119290-65-2**, Ro 23-7498 153088-24-5, Ro 25-8272 165811-43-8, Ro 25-9022 195527-19-6, Ro 26-2198
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT 61476-45-7 247244-88-8, Ro 25-4020
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT 56142-94-0 76338-50-6 97903-37-2 111820-83-8 151136-06-0 343770-67-2 343770-68-3 343970-33-2
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
IT 7440-70-2, calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism, vitamin D3 analogs effect on; highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(2) Baggiolini, E; J Org Chem 1986, V51, P3098 HCAPLUS
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(17) Reddy, G; Biochemistry 1989, V28, P1763 HCAPLUS
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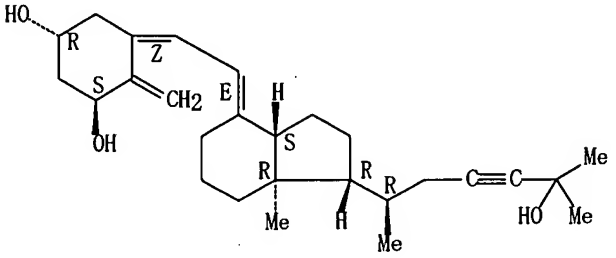
(22) Siu-Caldera, M; J Steroid Biochem Molec Biol 1996, V59(5/6), P405 HCAPLUS
(23) Sunita Rao, D; Steroids 2001, V66, P423 HCAPLUS
(24) Uskokovic, M; Vitamin D 1997, P1045 HCAPLUS
IT **119290-65-2**, Ro 23-7498

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(highly active analogs of dihydroxyvitamin D3 that resist metabolism through C-24 oxidation and C-3 epimerization pathways)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L17 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:513706 HCAPLUS
DN 122:248329
ED Entered STN: 28 Apr 1995
TI pharmaceutical compositions containing trans-retinoic acid and vitamin D3 analogs for leukemia
IN Dore, Benoit Thomas; Monparler, Richard Lewis
PA **Hoffmann-La Roche**, F., und Co. A.-G., Switz.
SO Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K031-59
ICS A61K031-07
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 07002674	A2	19950106	JP 1992-301557	19921015
PRAI US 1992-958399	A	19921008		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
JP 07002674	ICM	A61K031-59
	ICS	A61K031-07

AB Pharmaceutical compns. for leukemia contain trans-retinoic acid and vitamin D analogs. Thus, capsules were formulated containing trans-retinoic acid 5.00, 1α,25-dihydroxy-26,27-hexafluorocholecalciferol 0.005, beeswax 7.850, hardened soybean oil 7.850, hardened vegetable oil 31.40, BHA 0.11, soybean oil 112.285, and di-Na EDTA 0.50mg/capsule. Trans-retinoic acid and vitamin D3 analogs showed synergistic effect.
ST pharmaceutical leukemia retinoate vitamin D analog
IT Pharmaceutical dosage forms
(capsules, pharmaceutical compns. containing trans-retinoic acid and vitamin D3 analogs for leukemia)
IT Neoplasm inhibitors
(leukemia, pharmaceutical compns. containing trans-retinoic acid and vitamin D3 analogs for leukemia)
IT 67-97-0DP, Vitamin D3, analogs 302-79-4P, Trans-Retinoic acid 162581-21-7P 162581-22-8P 162581-23-9P 162581-24-0P **162581-25-1P** 162581-26-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical compns. containing trans-retinoic acid and vitamin D3 analogs for leukemia)

IT **162581-25-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pharmaceutical compns. containing trans-retinoic acid and vitamin D3 analogs for leukemia)

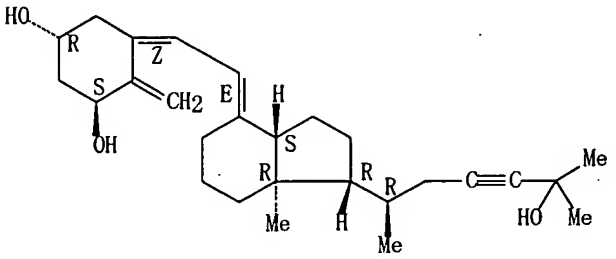
RN 162581-25-1 HCAPLUS

CN Retinoic acid, mixt. with (1α,3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 119290-65-2
CMF C27 H40 O3

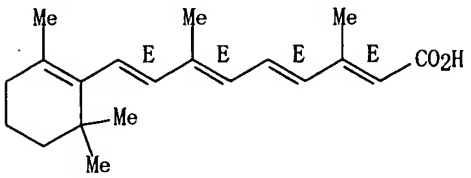
Absolute stereochemistry.
Double bond geometry as shown.



CM 2

CRN 302-79-4
CMF C20 H28 O2

Double bond geometry as shown.



L17 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:48355 HCAPLUS
DN 112:48355
ED Entered STN: 17 Feb 1990
TI Effects of vitamin D derivatives on soft tissue calcification in neonatal and calcium mobilization in adult rats
AU Kistler, Andreas; Galli, Brigitta; Horst, Ronald; Truitt, Gary A.; Uskokovic, Milan R.
CS F. **Hoffmann-La Roche** und Co. Ltd., Basel, CH-4002, Switz.
SO Archives of Toxicology (1989), 63(5), 394-400
CODEN: ARTODN; ISSN: 0340-5761
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The activity of 18 vitamin D analogs on soft tissue calcification and growth impairment in neonatal rats and their effect on bone calcium mobilization, intestinal calcium absorption and binding to intestinal 1,25-dihydroxyvitamin D3 receptors in adult rats were compared. Depending on the chemical modification of the vitamin D parent compds., they could be

separated into active and inactive analogs. Cholecalciferol and ergocalciferol were similarly active, but epimerization of ergocalciferol at C-23 caused loss of activity. Hexafluorination at C-26 and -27 and the introduction of a double bond at C-22 or -23 had no or little effect on the activity. The loss of activity was caused by the introduction of a triple bond at C-23 and by hydroxylation at C-23, -26 or -28. The differentiation of human promyelocytic leukemia cells (HL-60) induced by these derivs. was used as a parameter for antitumor activity. All 6 analogs which markedly affected calcium metabolism were highly active in HL-60 cells. However, ≥3 derivs. were highly active in the antitumor test but failed to induce hypercalcemia. Thus, these results indicate that it could be possible to develop medically useful vitamin D derivs. devoid of hypercalcemic side-effects.

ST vitamin D deriv tissue calcification antitumor

IT Newborn
(calcification in soft tissue in, vitamin D derivs. effect on, neoplasm-inhibiting activity in relation to)

IT Intestine, metabolism
(calcium absorption by, vitamin D derivs. effect on, dihydroxyvitamin D3 receptor binding in)

IT Bone, metabolism
(calcium metabolism by, vitamin D derivs. effect on)

IT Animal growth
(of newborn, vitamin D derivs. effect on, neoplasm-inhibiting activity in relation to)

IT Calcification
(of soft tissue, vitamin D derivs. effect on, in newborn, neoplasm inhibition in relation to)

IT Toxicity
(of vitamin D derivs., calcification of soft tissue and calcium mobilization in)

IT Neoplasm inhibitors
(vitamin D3 derivs. as, calcification of soft tissues and calcium mobilization in relation to)

IT Animal tissue
(soft, disease, calcification, from vitamin D derivs., in newborn, neoplasm-inhibiting activity in relation to)

IT Molecular structure-biological activity relationship
(toxic, of vitamin D derivs.)

IT 1406-16-2D, Vitamin D, derivs. 32222-06-3, Ro 21-5535 55721-11-4, Ro 21-5816 60133-18-8, Ro 17-6218 83805-11-2, Ro 23-4194 91874-90-7, Ro 23-6710 95783-08-7 101558-90-1, Ro 23-4319 103335-39-3, Ro 23-8525 103420-55-9, Ro 23-6005 104797-38-8, Ro 23 6536 104797-41-3, Ro 23-6869 104870-37-3, Ro 23-6474 118694-43-2, Ro 23-7553 118904-48-6, Ro 23-7982 **119290-65-2**, Ro 23-7498 119290-66-3, Ro 23-9375 121664-10-6, Ro 23-9360 122619-92-5, Ro 23-5112
RL: BIOL (Biological study)
(calcification in soft tissue in newborn and calcium mobilization in adults response to, neoplasm-inhibiting activity in relation to)

IT 7440-70-2
RL: BIOL (Biological study)
(calcification, of soft tissue, vitamin D derivs. effect on, in newborn, neoplasm inhibition in relation to)

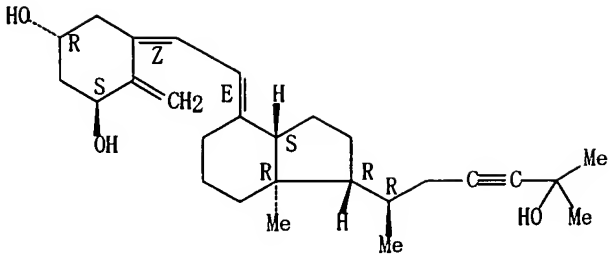
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by bone and intestine, vitamin D derivs. effect on)

IT **119290-65-2**, Ro 23-7498
RL: BIOL (Biological study)
(calcification in soft tissue in newborn and calcium mobilization in adults response to, neoplasm-inhibiting activity in relation to)

RN 119290-65-2 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



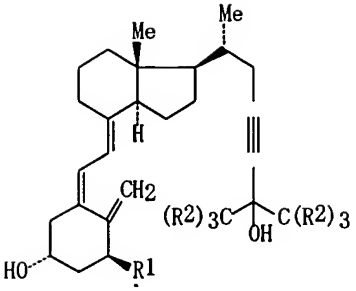
L17 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:458160 HCAPLUS
DN 111:58160
ED Entered STN: 20 Aug 1989
TI Cholecalciferol 23-yne derivatives, their pharmaceutical compositions, their use in the treatment of calcium-related diseases, and their antitumor activity
IN Baggiolini, Enrico G.; Partridge, John J.; Shiuey, Shian Jan; Truitt, Gary A.; Uskokovic, Milan R.
PA **Hoffmann-La Roche**, Inc., USA
SO U.S., 12 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07J009-00
INCL 260397200
CC 32-7 (Steroids)
Section cross-reference(s): 2
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4804502	A	19890214	US 1988-145867	19880120
	ZA 8900022	A	19890927	ZA 1989-22	19890103
	DK 8900196	A	19890721	DK 1989-196	19890117
	DK 171966	B1	19970901		
	CA 1314906	A1	19930323	CA 1989-588385	19890117
	HU 49316	A2	19890928	HU 1989-174	19890118
	HU 201736	B	19901228		
	IL 88988	A1	19930818	IL 1989-88988	19890118
	AU 8928643	A1	19890720	AU 1989-28643	19890119
	AU 621851	B2	19920326		
	FI 8900282	A	19890721	FI 1989-282	19890119
	FI 92193	B	19940630		
	FI 92193	C	19941010		
	NO 8900240	A	19890721	NO 1989-240	19890119
	NO 174547	B	19940214		
	NO 174547	C	19940525		
	JP 02009860	A2	19900112	JP 1989-8781	19890119
	JP 07064805	B4	19950712		
	EP 326875	A1	19890809	EP 1989-100973	19890120
	EP 326875	B1	19920325		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AT 74125	E	19920415	AT 1989-100973	19890120
	ES 2032613	T3	19930216	ES 1989-100973	19890120
PRAI	US 1988-145867	A	19880120		
	EP 1989-100973	A	19890120		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 4804502	ICM	C07J009-00
	INCL	260397200
US 4804502	NCL	514/167.000; 552/653.000; 556/428.000; 556/443.000; 556/446.000; 556/486.000

OS MARPAT 111:58160
GI



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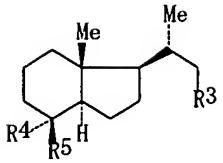


II

AB Vitamin D derivs. I (R1 = H, OH; R2 = H, F) are prepared for treatment of diseases involving metabolic Ca deficiencies. A precursor dimethyl[[(dimethylethyl)dimethylsilyl]oxy]octahydroindeneethanol (II; R3 = OH, R4 = H, R5 = OSiMe2CMe3) was treated with tosyl chloride in pyridine to give 96% II (R3 = tosyloxy), which reacted with LiC.tplbond.CSiMe3 to give 88% II (R3 = C.tplbond.CSiMe3). This was treated with AgNO3 in aqueous EtOH and then aqueous KCN to give 95% II (R3 = C.tplbond.CH), which was lithiated by BuLi and alkylated by CF3COCF3 to give 99% II [R3 = C.tplbond.CC(OH)(CF3)2, R4 = H, R5 = OSiMe2CMe3]. This was deprotected by HF in THF-MeCN (99%) and oxidized with 2,2'-bipyridinium chlorochromate to give II [R3 = C.tplbond.CC(OH)(CF3)2, R4R5 = O], which underwent Wittig reaction with a corresponding silyl-protected (dihydroxymethylenecyclohexylideneethyl)diphenylphosphine oxide (87%) and deprotection with Bu4NF (98%) to give I (R1 = OH, R2 = F) (III). Compared to 1,25-dihydroxyvitamin D3 in rats, III produced 124% of intestinal Ca absorption and 0% bone Ca mobilization.

ST cholecalciferol prepn calcium antitumor

IT Neoplasm inhibitors
(cholecalciferol yne derivs.)

IT 9,10-Secosteroids
RL: RCT (Reactant); RACT (Reactant or reagent)
(cholecalciferol yne derivs.)

IT Animal cell
(differentiation of, cholecalciferol yne derivs. effect on)

IT Receptors
RL: RCT (Reactant); RACT (Reactant or reagent)
(of dihydroxyvitamin D3, binding of cholecalciferol yne derivs. to)

IT Osteoporosis
(treatment of, cholecalciferol yne derivs. for)

IT Neoplasm inhibitors
(leukemia, cholecalciferol yne derivs.)

IT 7440-70-2P, Calcium, preparation
RL: PREP (Preparation)
(metabolic deficiencies of, cholecalciferol yne derivs. for treatment of)

IT 66774-80-9P 100928-04-9P 121664-12-8P 121664-13-9P 121664-14-0P 121664-15-1P 121664-16-2P 121664-17-3P 121664-18-4P 121664-19-5P 121664-20-8P 121664-21-9P 121664-22-0P 121664-23-1P 121664-24-2P 121664-25-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of cholecalciferol derivs.)

IT 1406-16-2DP, Vitamin D, derivs.
RL: PREP (Preparation)
(preparation of, for treatment of calcium deficiencies)

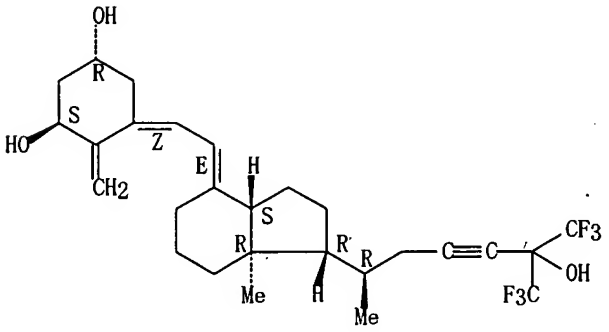
IT 119290-66-3P **121664-09-3P** 121664-10-6P **121664-11-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for treatment of calcium deficiency)

IT 684-16-2, Hexafluoroacetone 1066-54-2, Trimethylsilylacetylene 27943-46-0 64190-52-9 81522-68-1 100858-27-3 100928-03-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of cholecalciferol derivs.)

IT 32222-06-3, 1,25-Dihydroxyvitamin D3
RL: RCT (Reactant); RACT (Reactant or reagent)
(receptors of, binding of cholecalciferol yne derivs. to)

IT **121664-09-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for treatment of calcium deficiency)
RN 121664-09-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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L21 ANSWER 1 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:300266 HCAPLUS
DN 142:355450
ED Entered STN: 07 Apr 2005
TI Preparation and formulation of vitamin D derivatives for treating bladder dysfunction
IN Colli, Enrico
PA Bioxell, Inc., USA
SO PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-59
ICS C07C401-00
CC 32-7 (Steroids)
Section cross-reference(s): 1, 63
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005030223	A1	20050407	WO 2004-US31532	20040924 <--

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

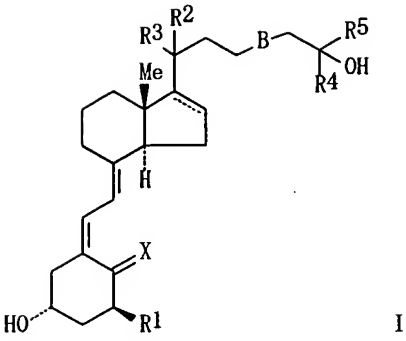
PRAI GB 2003-22395	A	20030924 <--	
GB 2003-25598	A	20031103 <--	
GB 2004-4567	A	20040301 <--	
GB 2004-4571	A	20040301 <--	
GB 2004-16876	A	20040729 <--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2005030223	ICM	A61K031-59

ICS C07C401-00

GI



I

AB Vitamin D derivs. of formula I [X = H2, CH2; R1 = H, OH, F; R2, R3 = H, Me; R4, R5 = Me, Et, CF3; B = single, double or triple bond] are prepared There is provided according to the invention the use of vitamin D compds. such as 1α-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol (II) in the prevention or treatment of bladder dysfunction. II had -Log IC50 of 11.2 with maximum tolerated dose of 100 μg/kg in stromal bladder cell model.

ST vitamin D deriv prepn formulation bladder dysfunction treatment

IT Drug delivery systems
(capsules, soft; preparation of vitamin D derivs. for treating bladder dysfunction)

IT Bladder, disease
(overactive bladder; preparation of vitamin D derivs. for treating bladder dysfunction)

IT Bladder, disease
Human
(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 9,10-Secosteroids
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 848945-47-1P 848945-48-2P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 770714-46-0P 770714-56-2P 792959-46-7P 848945-17-5P 848945-18-6P
848945-19-7P 848945-20-0P 848945-21-1P 848945-22-2P 848945-23-3P
848945-24-4P 848945-25-5P 848945-26-6P 848945-27-7P 848945-28-8P
848945-29-9P 848945-30-2P 848945-31-3P 848945-32-4P 848945-33-5P
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848945-39-1P 848945-40-4P 848945-41-5P 848945-42-6P 848945-43-7P
848945-44-8P 848945-45-9P 848945-46-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 199798-84-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 67-64-1, Acetone, reactions 873-55-2, Sodium benzenesulfinate
882-33-7, Diphenyldisulfide 118694-43-2 **119290-65-2**
124409-57-0 124409-58-1 137102-93-3 156208-06-9 195527-19-6
212844-16-1 215714-85-5 215714-88-8 221046-03-3 221046-04-4
221046-06-6 221046-09-9 221046-10-2 256459-48-0 848945-49-3
848945-50-6 848945-73-3
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of vitamin D derivs. for treating bladder dysfunction)

IT 684-16-2P, Hexafluoroacetone 81522-68-1P 139356-39-1P 713521-66-5P
713521-72-3P 713521-95-0P 770714-47-1P 770714-48-2P 770714-49-3P
770714-50-6P 770714-51-7P 770714-52-8P 770714-53-9P 770714-54-0P
770714-57-3P 792959-53-6P 792959-54-7P 792959-55-8P 792959-58-1P
792959-59-2P 792959-60-5P 792959-61-6P 792959-62-7P 792959-63-8P
792959-64-9P 792959-65-0P 792959-66-1P 792959-67-2P 792959-68-3P
792959-69-4P 792959-70-7P 792959-71-8P 792959-72-9P 792959-74-1P
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848945-77-7P 848945-78-8P 848945-79-9P 848945-80-2P 848945-81-3P
848945-82-4P 848945-83-5P 848945-84-6P 848945-85-7P 848945-86-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of vitamin D derivs. for treating bladder dysfunction)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

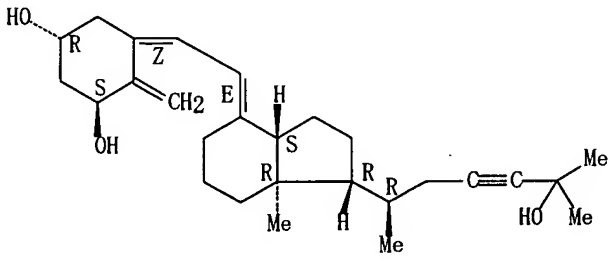
(1) Bishop; US 6566353 B2 2003 HCAPLUS

IT **119290-65-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of vitamin D derivs. for treating bladder dysfunction)

RN 119290-65-2 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:976708 HCAPLUS

DN 142:33275

ED Entered STN: 16 Nov 2004

TI The vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3 in vivo and in vitro

AU Huhtakangas, Johanna A.; Olivera, Christopher J.; Bishop, June E.; Zanello, Laura P.; Norman, Anthony W.

CS Department of Biochemistry, University of California, Riverside, CA, 92521, USA

SO Molecular Endocrinology (**2004**), 18(11), 2660-2671
CODEN: MOENEN; ISSN: 0888-8809

PB Endocrine Society

DT Journal

LA English

CC 2-10 (Mammalian Hormones)

AB The steroid hormone 1α,25(OH)2-vitamin D3 (1,25D) regulates gene transcription through a nuclear receptor [vitamin D receptor (VDR)] and initiation of rapid cellular responses through a putative plasma membrane-associated receptor (VDRmem). This study characterized the VDRmem present in a caveolae-enriched membrane fraction (CMF), a site of accumulation of signal transduction agents. Saturable and specific [3H]-1,25D binding in vitro was found in CMF of chick, rat, and mouse intestine; mouse lung and kidney; and human NB4 leukemia and rat ROS 17/2.8 osteoblast-like cells; in all cases the 1,25D KD binding dissociation constant = 1-3 nm. Our data collectively support the classical VDR being

the VDRmem in caveolae: (1) VDR antibody immunoreactivity was detected in CMF of all tissues tested; (2) competitive binding of [3H]-1,25D by eight analogs of 1,25D was significantly correlated between nuclei and CMF (r2 = 0.95) but not between vitamin D binding protein (has a different ligand binding specificity) and CMF; (3) confocal immunofluorescence microscopy of ROS 17/2.8 cells showed VDR in close association with the caveolae marker protein, caveolin-1, in the plasma membrane region; (4) in vivo 1,25D pretreatment reduced in vitro [3H]-1,25D binding by 30% in chick and rat intestinal CMF demonstrating in vivo occupancy of the CMF receptor by 1,25D; and (5) comparison of [3H]-1,25D binding in VDR KO and WT mouse kidney tissue showed 85% reduction in VDR KO CMF and 95% reduction in VDR KO nuclear fraction. This study supports the presence of VDR as the 1,25D-binding protein associated with plasma membrane caveolae.

ST dihydroxyvitamin D3 analog receptor caveolae cell membrane tissue caveolin

IT Organelle
(caveolae; vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(caveolins; vitamin D receptor is present in caveolae-enriched plasma membranes of tissues from VD-deficient chicks and mice, and binds 1α,25(OH)2-vitamin D3 in)

IT Intestine
(duodenum; vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3 in duodenum of chick and rat, ROS 17/2.8 and NB4 cells)

IT Kidney
Lung
(toxicity; vitamin D receptor is present in caveolae-enriched plasma membranes of tissues from VD-deficient chicks and mice, and binds 1α,25(OH)2-vitamin D3 in)

IT Cell membrane
Signal transduction, biological
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3)

IT Vitamin D receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3)

IT Human
Leukemia
Osteoblast
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3 in duodenum of chick and rat, ROS 17/2.8 and NB4 cells)

IT Intestine
Kidney
Lung
(vitamin D receptor is present in caveolae-enriched plasma membranes of tissues from VD-deficient chicks and mice, and binds 1α,25(OH)2-vitamin D3 in)

IT 32222-06-3, 1α,25-Dihydroxyvitamin D3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3)

IT 61954-91-4 72203-93-1 118694-43-2 134523-84-5 137171-69-8 168408-60-4 215257-70-8 **807374-44-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3 and analogs)

RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD

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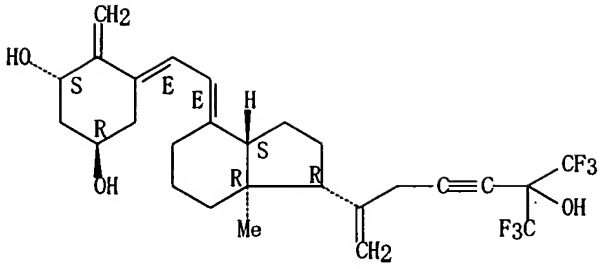
IT **807374-44-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1α,25(OH)2-vitamin D3 and analogs)

RN 807374-44-3 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19),20-tetraen-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,5E,7Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:886745 HCAPLUS
DN 142:17720
ED Entered STN: 26 Oct 2004
TI 1α,25-Dihydroxyvitamin D3 or analogue treated dendritic cells modulate human autoreactive T cells via the selective induction of apoptosis
AU van Halteren, Astrid G. S.; Tysma, Odette M.; van Etten, Evelyne; Mathieu, Chantal; Roep, Bart O.
CS Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, 2300 RC, Neth.
SO Journal of Autoimmunity (**2004**), 23(3), 233-239
CODEN: JOAUEP; ISSN: 0896-8411
PB Elsevier B.V.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 14, 15
AB Epidemiol. evidence indicates that the vitamin D status after birth modulates the risk for development of type 1 diabetes mellitus (T1DM). The authors previously demonstrated that the biol. active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), as well as its analog TX527 permanently alter the morphol. and T cell stimulatory function of human dendritic cells (DC). Here, the authors studied the mechanism of T cell modulation by 1,25(OH)2D3 or analog treated DC. By using CFSE-labeled autoreactive T cells, the authors observed that T cell proliferation is hampered upon coculture with modulated DCs, i.e. T cells underwent fewer cycles of cell divisions when compared to T cells stimulated by nontreated DCs. Moreover, 1,25(OH)2D3 or analog modulated DCs induced significantly higher nos. of early apoptotic (annexin V+/PI-) and/or late apoptotic (annexin V+/PI+) T cells. Apoptosis was selectively induced in T cells activated by modulated DC, since other T cells present in the same cultures, either resting or activated by control untreated DC, were unaffected. Thus, in vitro preconditioning of DC with 1,25(OH)2D3 or analog yields regulatory DC that may interfere with ongoing autoimmunity in vivo without affecting T cells with other specificities.
ST dihydroxyvitamin D3 analog dendritic cell autoreactive T cell apoptosis
IT Immunity
(autoimmunity; dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
IT Cell proliferation
(dihydroxyvitamin D or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
IT Apoptosis
Cell division
Dendritic cell
Human
Immunomodulators
T cell (lymphocyte)
(dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
IT Autoimmune disease
(insulin-dependent diabetes mellitus; dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis in relation to diabetes)

IT Diabetes mellitus
(insulin-dependent; dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis in relation to diabetes)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
IT 32222-06-3, 1α,25-Dihydroxyvitamin D3 **163379-89-3**, TX527
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
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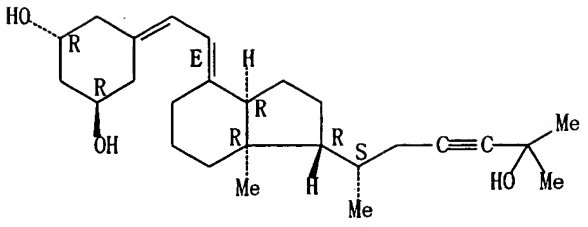
IT **163379-89-3**, TX527
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydroxyvitamin D3 or analog treated dendritic cells modulation of human autoreactive T cells via apoptosis)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:725745 HCAPLUS
DN 141:375033
ED Entered STN: 07 Sep 2004
TI Effect of 1,25(OH)2 Vitamin D3 Analogs on Differentiation Induction and Cytokine Modulation in Blasts from Acute Myeloid Leukemia Patients
AU Srivastava, Maya D.; Ambrus, Julian L.
CS Department of Pediatrics, Metro Health Medical Center, Cleveland, OH, 44109, USA
SO Leukemia & Lymphoma (**2004**), 45(10), 2119-2126
CODEN: LELYEA; ISSN: 1042-8194
PB Taylor & Francis Ltd.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB In acute myeloid leukemia (AML), cell proliferation and differentiation are uncoupled, causing a maturation block. Induction of terminal differentiation is a potential therapeutic strategy. 1α, 25(OH)2 Vitamin D3 regulates differentiation and is immunomodulatory at concns. causing severe hypercalcemia, thus limiting its use. We investigated 1α, 25(OH)2 Vitamin D3 and 5 of its more potent analogs with reduced calcium resorbing activity for differentiation of blast cells from AML (FAB M1) patients, compared to TPA. Blast phenotype, p-glycoprotein expression, cytokine production, and lineage specificity were examined The Vitamin D3 analogs had no effect on cell viability and proliferation. They induced incomplete differentiation, with increase in AP, NSE and NBT positivity of cells, but no cell sticking and spreading as observed with TPA. The analogs were more effective than the parent compound They also inhibited the production of IL-6 and IL-8. Vitamin D3 and its analogs can induce differentiation of primary cells from AML patients in vitro, but may need to be combined with other agents for terminal differentiation of blasts and effective therapy in vivo.
ST dihydroxyvitamin D3 analog cell differentiation cytokine blast myeloid leukemia
IT Leukemia
(acute myelogenous; effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT Cell differentiation
Human
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT Interleukin 6
Interleukin 8
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT B cell (lymphocyte)
T cell (lymphocyte)
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients and from B-, T-, and Eosinophilic leukemia cell lines)
IT Granuloma
(eosinophilic; effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients and from B-, T-, and Eosinophilic leukemia

cell lines)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT 83869-56-1, GM-CSF
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT 32222-06-3 104211-73-6 118694-43-2 **119290-65-2** 124409-58-1 781638-39-9
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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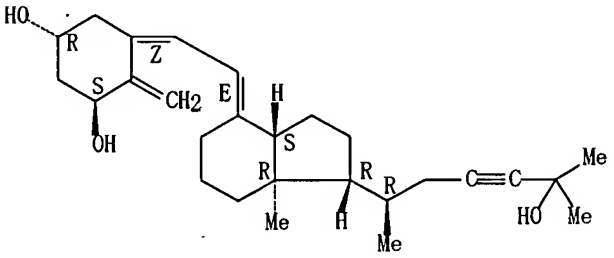
IT **119290-65-2**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of 1,25(OH)2 Vitamin D3 analogs on differentiation induction and cytokine modulation in blasts from acute myeloid leukemia patients)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:522242 HCAPLUS
DN 141:134635
ED Entered STN: 29 Jun 2004
TI NOD bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3
AU van Etten, Evelyne; Decallonne, Brigitte; Bouillon, Roger; Mathieu, Chantal
CS LEGENDO, O&N niv9, Katholieke Universiteit Leuven, Louvain, 3000, Belg.
SO Journal of Steroid Biochemistry and Molecular Biology (**2004**), 89-90(1-5), 457-459
CODEN: JSBBEZ; ISSN: 0960-0760
PB : Elsevier Science Ltd.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The immune effects of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) are mainly mediated through dendritic cells (DCs). In vitro, 1,25(OH)2D3 treatment renders murine bone marrow (BM)-derived DCs more tolerogenic, indirectly altering behavior and fate of T lymphocytes. In vivo, treatment with 1,25(OH)2D3 or its analogs prevents diabetes in NOD mice. The aim of this study was to investigate the effects of the 1,25(OH)2D3-analog TX527 on the expression of antigen-presenting and costimulatory/migratory mols. on BM-derived DCs from NOD mice. After culture with 20 ng/mL GM-CSF+20 ng/mL IL-4 (8 days) followed by 1000 ng/mL LPS+100 U/mL IFN-γ (2 days), with or without 10-8 M TX527, cells were counted and analyzed by FACS for MHC II, CD86, CD40 and CD54 expression within the CD11c+ DC population. Upon TX527 treatment, cell recovery was significantly reduced, whereas the CD11c+ DC fraction remained constant On CD11c+ DCs, MHC II, CD86 and CD54 were significantly down-regulated and CD40 was twofold upregulated. Globally, BM-derived DCs from NOD mice become more tolerogenic upon TX527 treatment, confirming the effects of 1,25(OH)2D3 on murine DCs and possibly explaining the protective effects of 1,25(OH)2D3 and its analogs from diabetes in NOD mice.
ST dihydroxyvitamin D3 TX527 bone marrow dendritic cell diabetes mouse
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD11C; murine nonobese diabetic bone marrow-derived dendritic cells

are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1); murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class II; murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Antidiabetic agents
Bone marrow
Dendritic cell
Diabetes mellitus
(murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT CD40 (antigen)
CD86 (antigen)
Interleukin 4
Lipopolysaccharides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Bone marrow
(toxicity; murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αX; murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT 83869-56-1, Granulocyte macrophage colony-stimulating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

IT 32222-06-3, 1,25-Dihydroxyvitamin D3 **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)

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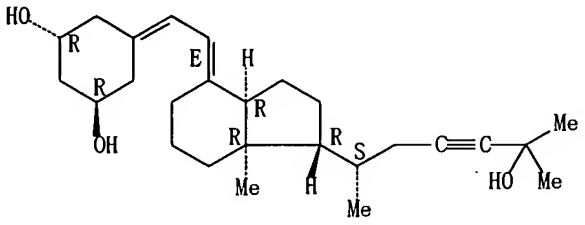
IT **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(murine nonobese diabetic bone marrow-derived dendritic cells are modulated by analogs of 1,25-dihydroxyvitamin D3 in relation to antidiabetic role)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:522239 HCAPLUS
DN 141:289377
ED Entered STN: 29 Jun 2004
TI Gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog
AU Griffin, Matthew D.; Xing, Nianzeng; Kumar, Rajiv
CS Department of Internal Medicine, Division of Nephrology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
SO Journal of Steroid Biochemistry and Molecular Biology (**2004**), 89-90(1-5), 443-448
CODEN: JSBBEZ; ISSN: 0960-0760
PB : Elsevier Science Ltd.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Inhibition of dendritic cell (DC) maturity is an important immunomodulatory effect of 1α,25-dihydroxyvitamin D3 (1α,25(OH)2D3) and related analogs (D3 analogs). The mechanisms underlying 1α,25(OH)2D3-mediated DC modulation are Vitamin D receptor (VDR)-dependent and likely involve direct or indirect regulation of multiple genes. Gene expression profiles of bone marrow-derived DCs (BMDCs) generated in the absence or presence of a potent D3 analog were analyzed using microarray technol. Results for D3 analog-conditioned DCs were also compared with glucocorticoid-conditioned BMDCs and with BMDCs conditioned with D3 analog and glucocorticoid combined. Of .apprx.12,000 gene products assayed, 52% were considered to have detectable expression in unconditioned BMDCs. Based on relative expression levels, 5.3% of these expressed genes were "silenced" or "suppressed" in D3 analog-conditioned BMDCs and 2.1% were "augmented". In addition, 1.7% of gene products undetectable in control BMDCs were "induced" by D3 analog. Functional grouping of modulated genes demonstrated important effects of D3 analog on immunoreceptors, on chemokines and chemokine receptors, on growth factors/cytokines and related receptors, and on neuroendocrine hormones and related receptors. Many of these gene products were unaffected or differently regulated by glucocorticoid suggesting specific VDR-mediated regulatory effects. Confirmation of microarray anal. results for two differentially regulated chemokines (MIP-1α and RANTES) was obtained by RT-PCR and ELISA. The methodol. provides novel insights into DC gene regulation by 1α,25(OH)2D3 agonists.
ST gene expression profile dendritic cell lalpha 25dihydroxyvitamin D3 glucocorticoid
IT Bone marrow

(-derived dendritic cells; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Microarray technology
(Affymetrix U74A microarray; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Dendritic cell
(bone marrow-derived; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Glucocorticoids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profile in response to, compared to 1α,25-dihydroxyvitamin analog; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Gene expression profiles, animal
(gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Macrophage inflammatory protein 1α
Platelet-derived growth factors
RANTES (chemokine)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Chemokine receptors
Chemokines
Cytokine receptors
Cytokines
Growth factor receptors
Growth factors, animal
Immunoglobulin receptors
Neurohormone receptors
Neurohormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(genes regulating; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Bone marrow
(toxicity, -derived dendritic cells; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Fibroblast growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 1; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β3-; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT 32222-06-3, 1α,25-Dihydroxyvitamin D3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(analog; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT 50-02-2, Dexamethasone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profile in response to, compared to 1α,25-dihydroxyvitamin analog; gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
IT **762303-09-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
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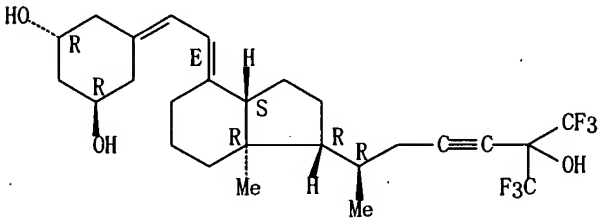
IT **762303-09-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiles in dendritic cells conditioned by 1α,25-dihydroxyvitamin D3 analog)

RN 762303-09-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:483412 HCAPLUS

DN 142:33087

ED Entered STN: 16 Jun 2004

TI Relationship between differentiation-inducing activity and hypercalcemic activity of hexafluorotrihydroxyvitamin D3 derivatives

AU Unten, Senwa; Ishihara, Mariko; Sakagami, Hiroshi

CS Department of Dental Pharmacology, Meikai University School of Dentistry, Sakado, Saitama, 350-0283, Japan

SO Anticancer Research (**2004**), 24(2B), 683-689
CODEN: ANTRD4; ISSN: 0250-7005

PB International Institute of Anticancer Research

DT Journal

LA English

CC 2-2 (Mammalian Hormones)
Section cross-reference(s): 1

AB Among 16 newly synthesized hexafluoro trihydroxyvitamin D3 derivs., 24-Homo-26,26,26,27,27,27 hexafluoro (24H-F6)-1,24(S), 25(OH)3 vitamin D3 (VD3)(DD-011)[16] induced differentiation (i.e., appearance of NBT-pos. cells) of human. Promyelocytic leukemic HL-60 cells most efficiently (EC50=0.5 nM), followed by 24H-F6-1,25(OH)2-22-oxa-VD3 (DD-006) [11] > F6-1,25(OH)2-VD3 (F6VD3) [2] > F6-1,25(OH)2-22-ene-VD3. (DD-009) [14] > 24H-F6-1,25(OH)2-VD3 (F6C28) [3] > 24H-F6-1,25(OH)2 1,23(S),25(OH)3-VD3 (DD-015) [18] > 24H-F6-1,25(OH)2-22-ene-VD3 (mvd1400) [6] > 22H-F6-1,25(OH)2-24-ene-VD3 (mvd3400) [5] > 24H-F6-1,23(R),25(OH)3-VDABS 013 (DD-014) [17] > 24H-F6-1,22(S),25(OH)3-VD3 (DD-003) [7] > 24H-F6-1,22(S),25(OH)3-24-yne-VD3 (DD-005) [9] > 24H-F6-1,22(R),25(OH)3-24-yne-VD3 (mvd-1235) [10] > F6-1,25(OH)2-22-ene-VD3 (DD-008) [13] = 1,25(OH)2VD3 [1] (CC50=6 nM). On the other hand, 24H-F6-1,22(R),25(OH)3-VD3 (DD-004) [8], which is an isomer of DD-003 [7], showed much reduced activity (CC50=100 nM), suggesting the importance of the configuration of the OH group at the C-22. When their differentiation-inducing activity was plotted vs. the octanol-water partition coefficient (log P) used as a parameter of hydrophobicity, a bell-shaped curve was produced, with the bottom at log P=5.4-5.8. There was no clear-cut relationship between the differentiation-inducing activity and hypercalcemic activity (serum calcium elevating activity). Compds. [3, 7, 11, 17] showed relatively higher differentiation-inducing activity, with lesser hypercalcemic activity, as compared with [1]. Administration of [7] showed potent antiproliferation activity against colon cancer transplanted in nude mice. These results further confirmed the antitumor potential of

hexafluorotrihydroxyvitamin D3 derivs.

ST hexafluorotrihydroxyvitamin D3 cell differentiation hypercalcemic structure activity relationship antitumor

IT Antitumor agents
(24H-F6-1,22(S),25(OH)3-VD3 administration exerted antitumor activity by reducing growth rate of human colon cancer HT-29 and also prolonged survival time of mice transplanted with mouse leukemic cells)

IT Cell differentiation
(24H-F6-1,24(S),25(OH)3-VD3 among other 18 hexafluorotrihydroxyvitamin D3 derivs. showed highest differentiation-inducing activity against human promyelocytic leukemic HL-60 cells)

IT Human
(24H-F6-1,24(S),25(OH)3-VD3 showed highest differentiation-inducing activity and 24H-F6-1,22(R),25(OH)3-VD3showed lowest hypercalcemic activity against human promyelocytic leukemic HL-60 cells)

IT Animal cell line
(HL-60; 24H-F6-1,24(S),25(OH)3-VD3 showed highest differentiation-inducing activity and 24H-F6-1,22(R),25(OH)3-VD3showed lowest hypercalcemic activity against human promyelocytic leukemic HL-60 cells)

IT Intestine, neoplasm
(colon; 24H-F6-1,22(S),25(OH)3-VD3 administration exerted antitumor activity by reducing growth rate of human colon cancer HT-29 and also prolonged survival time of mice transplanted with mouse leukemic cells)

IT Structure-activity relationship
(differentiation-inducing activity and hypercalcemic activity by different hexafluorotrihydroxyvitamin D3 derivs. on promyelocytic leukemic HL-60 cells could be attributed to their structural activity relationship)

IT Leukemia
(promyelocytic; 24H-F6-1,24(S),25(OH)3-VD3 showed highest differentiation-inducing activity and 24H-F6-1,22(R),25(OH)3-VD3showed lowest hypercalcemic activity against human promyelocytic leukemic HL-60 cells)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(24H-F6-1,22(R),25(OH)3-VD3 among other 18 hexafluorotrihydroxyvitamin D3 derivs. showed lowest hypercalcemic activity against promyelocytic leukemic HL-60 cells)

IT 32222-06-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, 1,25(OH)2VD3 induced differentiation of HL-60 cells, showed higher NBT-reducing activity, lower proliferation activity and increased serum calcium concentration in dose dependent manner)

IT 791817-37-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-0010 showed higher differentiation-inducing activity, hypercalcemic activity and also inhibited growth of HL-60 cells)

IT 791817-38-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-0011 showed greatest differentiation-inducing activity and higher hypercalcemic activity and also inhibited growth of HL-60 cells)

IT 173175-54-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-0014 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells suggesting its potential in treatment of cancer)

IT 173243-40-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-0015 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells compared to 1,25(OH)2VD3)

IT 143167-85-5, DD-003
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-003 showed higher differentiation-inducing activity, lesser hypercalcemic activity against HL-60 cell and significantly reduced growth rate of human colon cancer HT-29 cell in mouse)

IT 143101-70-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-004 isomer of DD-003 showed much reduced differentiation-inducing activity and lowest hypercalcemic activity than other derivs. against HL-60 cells)

IT 144177-02-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-005 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells compared to 1,25(OH)2VD3)

IT 791817-36-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-006 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells suggesting its potential in treatment of cancer)

IT 152825-69-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-007 showed higher hypercalcemic activity but very weak differentiation-inducing activity in HL-60 cells)

IT 156078-61-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-008 showed differentiation-inducing activity, higher hypercalcemic activity and also inhibited growth of HL-60 cells)

IT 156196-99-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, DD-009 showed higher differentiation-inducing activity, higher hypercalcemic activity and also inhibited growth of HL-60 cells)

IT 83805-11-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, F61,25(OH)2VD3 showed higher differentiation-inducing activity, higher hypercalcemic activity and also inhibited growth of HL-60 cells)

IT 151644-56-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, F61,25(OH)2VD3C28 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells suggesting its potential in treatment of cancer)

IT 151644-57-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, F61,25(OH)2VD3C29 showed less differentiation-inducing activity and hypercalcemic activity against HL-60 cells)

IT **144100-33-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, MVD-1235 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells compared to 1,25(OH)2VD3)

IT 149008-26-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(hexafluorotrihydroxyvitamin D3 derivative, MVD-1400 showed higher differentiation-inducing activity and inhibited HL-60 cell growth more potently than 1,25(OH)2VD3)

IT 149008-31-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, MVD-3400 showed higher differentiation-inducing activity and inhibited HL-60 cell growth more potently than 1,25(OH)2VD3)

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD

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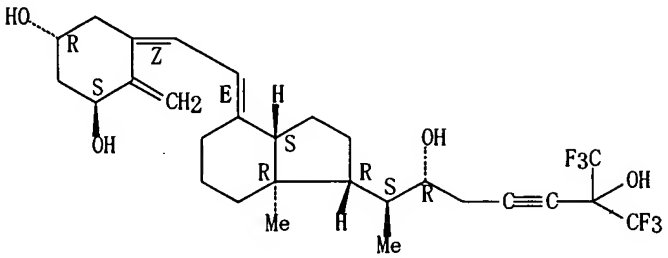
IT **144100-33-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hexafluorotrihydroxyvitamin D3 derivative, MVD-1235 showed higher differentiation-inducing activity and lesser hypercalcemic activity against HL-60 cells compared to 1,25(OH)2VD3)

RN 144100-33-4 HCAPLUS
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-7a-methyl-1-[(1S,2R)-7,7,7-trifluoro-2,6-dihydroxy-1-methyl-6-(trifluoromethyl)-4-heptynyl]-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:377834 HCAPLUS
DN 142:150920
ED Entered STN: 11 May 2004
TI Two 14-epi analogues of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB
AU De Haes, Petra; Garmyn, Marjan; Verstuyf, Annemieke; De Clercq, Pierre; Vandewalle, Maurits; Vantieghem, Katleen; Degreef, Hugo; Bouillon, Roger; Segaert, Siegfried
CS Laboratory for Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Louvain, 3000, Belg.
SO Archives of Dermatological Research (**2004**), 295(12), 527-534
CODEN: ADREDL; ISSN: 0340-3696
PB Springer-Verlag
DT Journal
LA English
CC 8-9 (Radiation Biochemistry)

AB In search of photoprotective agents, we recently demonstrated a protective effect of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] against different events mediated by UV B (UVB) in human keratinocytes. Pharmacol. doses of 1,25(OH)2D3 were required to obtain significant UVB protection; however, these doses cannot be used in vivo due to the calcemic properties of 1,25(OH)2D3. Therefore, we evaluated the photoprotective capacities of two low-calcemic 14-epi analogs of 1,25(OH)2D3, 19-nor-14-epi-23-yne-1,25(OH)2D3 (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25(OH)2D3 (TX 527). Using cultured human keratinocytes, we investigated the influence of TX 522 and TX 527 on two hallmark events in UVB-irradiated keratinocytes: the induction of apoptosis and the production of interleukin-6 (IL-6). Treatment of the keratinocytes with TX 522 or TX 527, 24 h before irradiation, resulted in a significant and dose-dependent reduction of both UVB-induced apoptosis and IL-6 production Both analogs were equally efficient in their anti-UVB effects and at least 100 times more potent than 1,25(OH)2D3. We further demonstrated that metallothionein (MT) mRNA expression was clearly induced by 1,25(OH)2D3 and both analogs. MT acts as a radical scavenger in oxygen-mediated UVB injury and its induction may therefore be relevant for the anti-UVB effects of 1,25(OH)2D3 and both analogs. Taken together, these findings create new perspectives for the use of active vitamin D analogs as photoprotective agents.

ST dihydroxy vitamin D3 analog UVB photoprotectant keratinocyte; antiproliferative UVB photoprotectant TX527 TX527

IT Apoptosis
Cell proliferation
(inhibition; two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

IT Skin
(keratinocyte; two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

IT Human
Photoprotectants
UV B radiation
(two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

IT Interleukin 6
Metallothioneins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

IT 32222-06-3, 1,25-Dihydroxyvitamin D3 **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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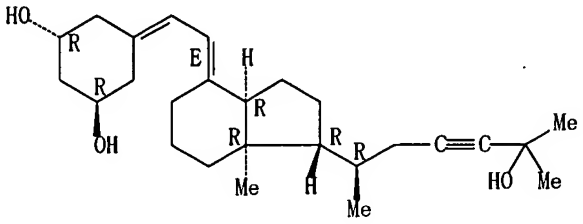
IT **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(two 14-epi analogs of 1,25-dihydroxyvitamin D3 protect human keratinocytes against the effects of UVB)

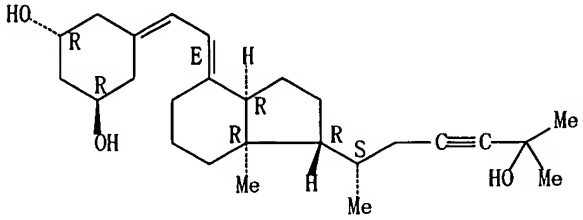
RN 163217-09-2 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:273505 HCAPLUS
DN 139:358288
ED Entered STN: 09 Apr 2003
TI Combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents experimental autoimmune encephalomyelitis and preserves bone
AU Van Etten, E.; Branisteanu, D. D.; Overbergh, L.; Bouillon, R.; Verstuyf, A.; Mathieu, C.
CS Laboratory of Experimental Medicine and Endocrinology, Catholic University of Leuven, Louvain, 3000, Belg.
SO Bone (New York, NY, United States) (**2003**), 32(4), 397-404
CODEN: BONEDL; ISSN: 8756-3282
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-7 (Pharmacology)

AB The vitamin D analog TX527 (19-nor-14,20-bis epi-23-yne-1,25(OH)2D3), decreased disease severity ($P < 0.001$) and postponed disease onset ($P < 0.0001$) in SJL mice in which exptl. autoimmune encephalomyelitis was induced. Levels of IFN-γ and IL-2 mRNA were decreased in spinal cord and spleen in the analog-treated mice, suggesting a Th1-targeted effect. Adding the bisphosphonate pamidronate did not affect analog-protective efficacy, but completely prevented TX527-induced acceleration of bone turnover and increased total bone mineral content as well as femoral mineral and calcium content ($P < 0.01$). Thus, Less calcemic analogs of 1,25-dihydroxyvitamin D3, in combination with bone sparing products such as bisphosphonates allow immune modulation in vivo without affecting bone.

ST immunomodulator dihydroxyvitamin D3 analog bisphosphonate exptl autoimmune encephalomyelitis bone; multiple sclerosis model immunomodulator TX527 bone sparing bisphosphonate

IT Multiple sclerosis
(animal model; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Immunosuppressants
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Interleukin 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression in spinal cord and spleen; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Interleukin 4
Osteocalcins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Autoimmune disease
(exptl. autoimmune encephalomyelitis; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Encephalomyelitis
(exptl. autoimmune; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT T cell (lymphocyte)
(helper cell/inducer, TH1; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Spinal cord
Spleen
(interferon-γ and interleukin-2 expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Bone formation
(mineralization; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Bone
(resorption; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, expression in spinal cord and spleen; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT 32222-06-3, 1,25-Dihydroxyvitamin D3 **163379-89-3**, TX527
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT 57248-88-1, Pamidronate disodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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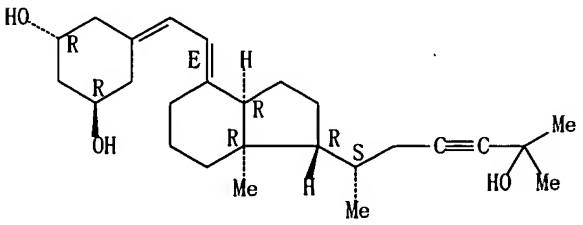
IT **163379-89-3**, TX527
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:73861 HCAPLUS

DN 138:315064
ED Entered STN: 30 Jan 2003
TI Analogs of 1α,25-dihydroxyvitamin D3 as pluripotent immunomodulators
AU Van Etten, Evelyne; Decallonne, Brigitte; Verlinden, Lieve; Verstuyf, Annemieke; Bouillon, Roger; Mathieu, Chantal
CS Laboratory for Experimental Medicine and Endocrinology, Catholic University of Leuven, Louvain, 3000, Belg.
SO Journal of Cellular Biochemistry (**2003**), 88(2), 223-226
CODEN: JCEBD5; ISSN: 0730-2312
PB Wiley-Liss, Inc.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The authors described the effects of the structural analog of 1α,25-dihydroxyvitamin D3 [1,25(OH)2D3] TX527 (19-nor-14,20-bisepi-23-yne-1-25-dihydroxyvitamin D3) on proliferation of human T lymphocytes, on differentiation of human dendritic cells, and on the development and recurrence of type 1 diabetes in nonobese diabetic mice. , In vitro TX527 is more potent that 1,25(OH)2D3 in redirecting differentiation and maturation of dendritic cells and in inhibiting phytohemagglutinin-stimulated T lymphocyte proliferation. In vivo, this enhanced potency of TX527 was confirmed by a stronger potential to prevent type 1 diabetes in nonobese diabetic mice and to prolong the survival of syngeneic islets grafts, both alone and in combination with cyclosporine A, in overtly diabetic NOD mice. Moreover, these in vivo effects of TX527 are obtained without the adverse side effects observed for 1,25(OH)2D3 itself. The authors believe that TX527 is a potentially interesting candidate to be considered for clin. trails in autoimmune diseases.
ST dihydroxyvitamin D3 analog TX527 immunomodulator; T lymphocyte proliferation TX527; dendritic cell differentiation TX527; diabetes type 1 TX527; pancreatic islet transplant TX527
IT Dendritic cell
Human
T cell (lymphocyte)
(epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Autoimmune disease
(insulin-dependent diabetes mellitus; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Diabetes mellitus
(insulin-dependent; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Cell proliferation
(of T lymphocyte; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Cell differentiation
(of dendritic cells; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Transplant and Transplantation
(pancreatic islet; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT Pancreatic islet of Langerhans
(transplant; epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
IT 32222-06-3, 1α,25-Dihydroxyvitamin D3 **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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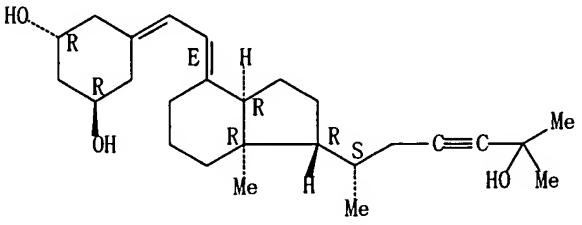
(14) Verlinden, L; J Bone Miner Res 2001, V16, P625 HCAPLUS
(15) Verstuyf, A; Expert Opin Investig Drugs 2000, V9, P443 HCAPLUS

IT **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epi-14 analog of 1α,25-dihydroxyvitamin D3 TX527 as pluripotent immunomodulator)

RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:521666 HCAPLUS
DN 137:242429
ED Entered STN: 12 Jul 2002
TI Redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3
AU Van Halteren, Astrid G. S.; Van Etten, Evelyne; De Jong, Esther C.; Bouillon, Roger; Roep, Bart O.; Mathieu, Chantal
CS Department of Immunohematology and Blood Transfusion, Leids Universitair Medisch Centrum, Leiden, 2300 RC, Neth.
SO Diabetes (**2002**), 51(7), 2119-2125
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 15
AB The active form of vitamin D3, 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), is a potent immunomodulator known to affect T-cells through targeting antigen-presenting cells such as dendritic cells (DCs). We studied the effects of a novel non-hypercalcemic 1,25(OH)2D3 analog, TX527, on DC differentiation, maturation, and function with respect to stimulation of a committed human GAD65-specific autoreactive T-cell clone. Continuous addition of TX527 impaired interleukin (IL)-4 and granulocyte/macrophage colony-stimulating factor (GM-CSF)-driven DC differentiation as well as lipopolysaccharide (LPS) and interferon-γ (IFN-γ)-induced maturation into Th1-promoting DC (DC1), as characterized by marked changes in DC morphol. and abrogation of IL-12p70 release upon CD40 ligation. Addition of TX527 during maturation did not affect DC morphol. but significantly changed DC cytokine profiles. The potential of treated DCs to alter the response pattern of committed autoreactive T-cells was found to depend on the timing of TX527 exposure. Continuously TX527-treated DCs significantly inhibited T-cell proliferation and blocked IFN-γ, IL-10, but not IL-13 production, whereas DCs treated during maturation failed to inhibit T-cell proliferation but affected IL-10 and IFN-γ production Collectively, we provide evidence that non-hypercalcemic TX527 is a potent in vitro DC modulator, yielding DCs with the potential to change cytokine responses of committed autoreactive T-cells.
ST T cell differentiation dendritic cell TX527 vitamin D3 analog

IT Cell proliferation
(T cell, inhibition by TX527-treated DC; redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT T cell (lymphocyte)
(helper cell/inducer, TH1; redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT Interleukin 12
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p70; redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT T cell (lymphocyte)
(proliferation, inhibition by TX527-treated DC; redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT Cell differentiation
Cell morphology
Immunomodulators
(redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT CD40 (antigen)
Cytokines
Interleukin 10
Interleukin 13
Interleukin 4
Lipopolysaccharides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT Dendritic cell
Human
T cell (lymphocyte)
(redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TX 527; redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT 83869-56-1, Granulocyte/macrophage colony-stimulating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(redirection of human autoreactive T-cells cytokine profile upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
IT 32222-06-3D, 1α,25-Dihydroxyvitamin D3, analogs
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
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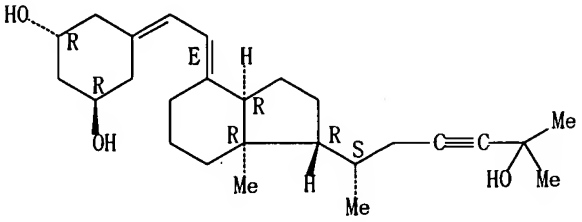
IT **163379-89-3**, TX527
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TX 527; redirection of human autoreactive T-cells upon interaction with dendritic cells modulated by TX527, an analog of 1,25 dihydroxyvitamin D3)

RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:467583 HCAPLUS

DN 137:261692

ED Entered STN: 23 Jun 2002

TI Treatment of autoimmune diabetes recurrence in non-obese diabetic mice by mouse interferon-β in combination with an analogue of 1α,25-dihydroxyvitamin-D3

AU Gysemans, C.; Van Etten, E.; Overbergh, L.; Verstuyf, A.; Waer, M.; Bouillon, R.; Mathieu, C.

CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven, Louvain, Belg.

SO Clinical and Experimental Immunology (**2002**), 128(2), 213-220
CODEN: CEXIAL; ISSN: 0009-9104

PB Blackwell Science Ltd.

DT Journal

LA English

CC 15-8 (Immunochemistry)

Section cross-reference(s): 1, 2

AB Autoimmune diabetes recurrence is in part responsible for islet graft destruction in type 1 diabetic individuals. The aim of the present study was to design treatment modalities able to prevent autoimmune diabetes recurrence after islet transplantation in spontaneously diabetic NOD mice. In order to avoid confusion between autoimmune diabetes recurrence and allograft rejection, the authors performed syngeneic islet transplantations in spontaneously diabetic NOD mice. Mice were treated with mouse interferon-β (IFN-β, 1+105 IU/day), a new 14-epi-1,25-(OH)2D3-analog (TX 527, 5 μg/kg/day) and cyclosporin A (CsA, 7.5 mg/kg/day) as single substances and in combinations. Treatment was stopped either 20 days (IFN-β and CsA) or 30 days (TX 527) after transplantation. Autoimmune diabetes recurred in 100% of control mice (MST 11 days). None of the mono-therapies significantly prolonged islet graft survival. Combining CsA with TX 527 maintained graft function in 67% of recipients as long as treatment was given (MST 31 days, vs. controls). Interestingly, 100% of the IFN-β plus TX 527-treated mice had normal blood glucose levels during treatment, and even had a more pronounced prolongation of graft survival (MST 62 days, vs. controls). Cytokine mRNA anal. of the grafts 6 days after transplantation revealed a significant decrease in IL-2, IFN-γ and IL-12 messages in both IFN-β plus TX 527- and CsA plus TX 527-treated mice, while only in the IFN-β with TX 527 group were higher levels of IL-10 transcripts observed Therefore, the authors conclude that a combination of IFN-β and TX 527 delays autoimmune diabetes recurrence in islet grafts in spontaneously diabetic NOD mice.

ST autoimmune diabetes interferon dihydroxyvitamin D3 islet transplantation

IT Transplant and Transplantation
(allotransplant, islet; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Pancreatic islet of Langerhans
(allotransplant; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT T cell (lymphocyte)
(helper cell/inducer, TH1; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Autoimmune disease
(insulin-dependent diabetes mellitus; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Diabetes mellitus
(insulin-dependent; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interleukin 10
Interleukin 12
Interleukin 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Drug interactions
(synergistic; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interferons
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT 59865-13-3, Cyclosporin A **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for

treatment of mouse autoimmune diabetes recurrence)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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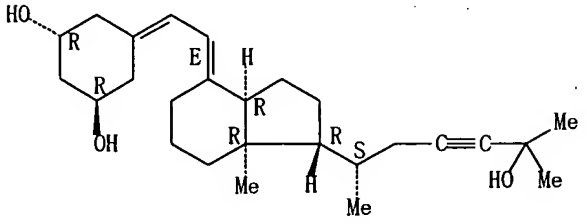
IT **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:790422 HCAPLUS
DN 136:85987
ED Entered STN: 31 Oct 2001

TI A practical synthesis of 14-epi-19-nor-1α,25-dihydroxyvitamin D3 analogues and their A-ring epimers
AU Wu, Yusheng; Zhao, Yurui; Tian, Honjian; De Clercq, Pierre; Vandewalle, Maurits; Berthier, Marielle; Pellegrino, Gills; Maillos, Philippe; Pascal, Jean-Claude
CS Laboratory of Organic Synthesis, Department of Organic Chemistry, University of Ghent, Ghent, 9000, Belg.
SO European Journal of Organic Chemistry (**2001**), (20), 3779-3788
CODEN: EJOCFK; ISSN: 1434-193X
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
CC 32-7 (Steroids)
OS CASREACT 136:85987
AB A practical synthesis of (2S,3aS,4aS)-2-(tert-butyldimethylsilyloxy)bicyclo[3.1.0]hexane-3a-carbaldehyde and diastereoisomers, starting from all-cis Me 3,5-dihydroxy-1-cyclohexanecarboxylate is described. Coupling with appropriate cis-hydrindanes produces the title compds. and is the key step in the syntheses. TX 522, a member of this series, is currently in phase II clin. studies for the treatment of psoriasis.
ST vitamin D3 analog prepn A ring epimer; coupling vitamin D3 analog prepn; dihydroxyvitamin D3 analog epimer prepn
IT Coupling reaction
(preparation of dihydroxyvitamin D3 analogs and their A-ring epimers via coupling with hydrindanes)
IT 157306-60-0 163217-26-3 183559-11-7 326598-94-1 326599-04-6
386766-78-5 386766-87-6 386766-88-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of dihydroxyvitamin D3 analogs and their A-ring epimers via coupling with hydrindanes)
IT 163217-22-9P 163217-23-0P 163217-24-1P 163217-25-2P 326599-01-3P
326599-02-4P 326599-06-8P 326599-09-1P 326599-33-1P 326599-34-2P
326599-39-7P 326599-40-0P 326599-42-2P 326599-44-4P 386766-74-1P
386766-75-2P 386766-77-4P 386766-79-6P 386766-80-9P 386766-81-0P
386766-84-3P 386766-85-4P 386766-86-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dihydroxyvitamin D3 analogs and their A-ring epimers via coupling with hydrindanes)
IT **163217-09-2P**, TX 522 163379-88-2P, KS 532 299410-91-6P
326599-37-5P 326599-47-7P 386766-76-3P 386766-82-1P 386766-83-2P
386766-89-8P 387352-55-8P 387357-66-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of dihydroxyvitamin D3 analogs and their A-ring epimers via coupling with hydrindanes)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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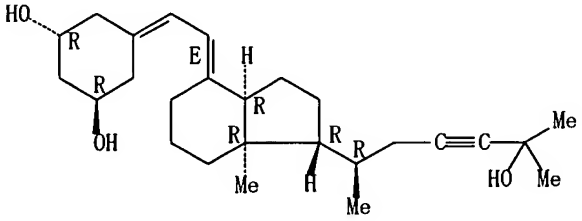
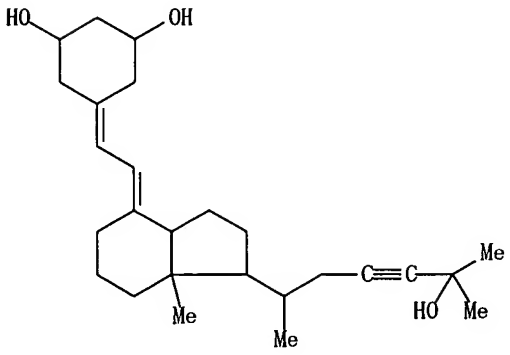
IT **163217-09-2P**, TX 522 **386766-89-8P 387352-55-8P 387357-66-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of dihydroxyvitamin D3 analogs and their A-ring epimers via coupling with hydrindanes)

RN 163217-09-2 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β)- (9CI) (CA INDEX NAME)

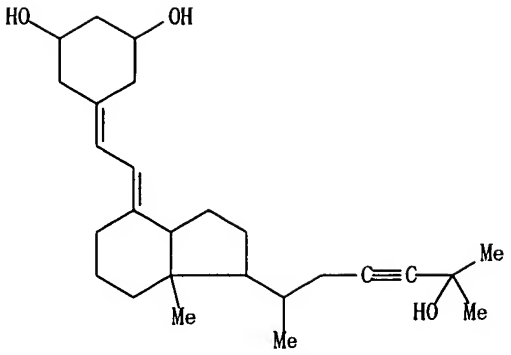
Absolute stereochemistry.
Double bond geometry as shown.



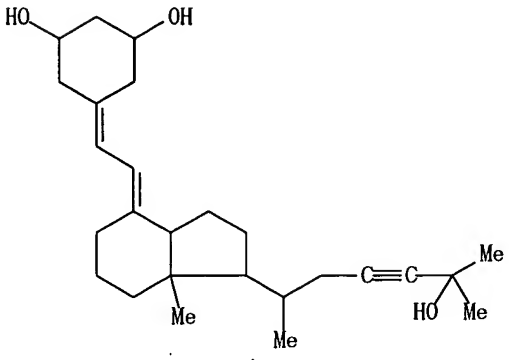
RN 386766-89-8 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3α,5Z,7Z,14β)- (9CI) (CA INDEX NAME)



RN 387352-55-8 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3α,5Z,7E,14β)- (9CI) (CA INDEX NAME)



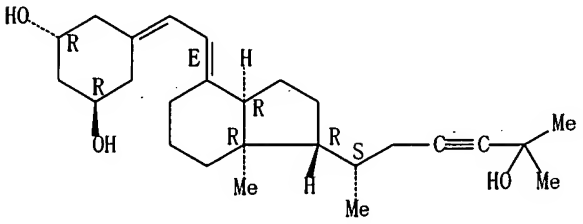
RN 387357-66-6 HCAPLUS
CN 19-Nor-9, 10-secocholesta-5, 7-dien-23-yne-1, 3, 25-triol, (1α, 3α, 5E, 7Z, 14β)- (9CI) (CA INDEX NAME)



L21 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:374037 HCAPLUS
DN 135:190779
ED Entered STN: 24 May 2001
TI Immunomodulatory properties of a 1,25(OH)2 vitamin D3 analog combined with IFNβ in an animal model of syngeneic islet transplantation
AU van Etten, E.; Gysemans, C.; Verstuyf, A.; Bouillon, R.; Mathieu, C.
CS Laboratory of Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Louvain, Belg.
SO Transplantation Proceedings (**2001**), 33(3), 2319
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1, 15
AB Immunomodulation obtained by combinations of TX527 (vitamin D3 analog), with interferon-β (IFNβ) and cyclosporin A (CyA) in syngeneic islet transplantation in spontaneously diabetic NOD mice was evaluated. All control mice showed disease recurrence within 2 wk after transplantation. The islet graft survival was not (TX527 and IFNβ) or only slightly (CyA) prolonged by monotherapies. Combination of TX527 with CyA and with IFNβ prolonged syngeneic graft survival.
ST TX527 interferon beta cyclosporin immunomodulation transplant
IT Immunomodulators
(immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Transplant and Transplantation
(pancreatic islet; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Drug interactions

(synergistic; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Pancreatic islet of Langerhans
(transplant; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT 59865-13-3, Cyclosporin A **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Van Etten, E; Transplantation 2000, V69, P1932 HCAPLUS
(2) Yong, W; Neurology 1998, V51, P682
IT **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:274738 HCAPLUS
DN 134:336425
ED Entered STN: 18 Apr 2001
TI Interaction of two novel 14-epivitamin D3 analogs with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements
AU Verlinden, Lieve; Verstuyf, Annemieke; Quack, Marcus; Van Camp, Mark; Van Etten, Evelyne; De Clercq, Pierre; Vandewalle, Maurits; Carlberg, Carsten; Bouillon, Roger
CS Laboratorium voor Experimentele Geneeskunde en Endocrinologie, Katholieke Universiteit Leuven, Louvain, Belg.
SO Journal of Bone and Mineral Research (**2001**), 16(4), 625-638
CODEN: JBMREJ; ISSN: 0884-0431
PB American Society for Bone and Mineral Research
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 3
AB This study provides a detailed and exact evaluation of the interactions between vitamin D3 receptor (VDR), retinoid X receptor (RXR), and vitamin D3 responsive elements (VDREs) mediated by two novel 14-epianalogs of 1,25-dihydroxyvitamin D [1,25(OH)2D3], 19-nor-14-epi-23-yne-1,25(OH)2D3 (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25(OH)2D3 (TX 527). Both

analogs were more potent (14- and 75-fold, resp.) than 1,25(OH)2D3 in inhibiting cell proliferation and inducing cell differentiation. However, DNA-independent expts. indicated that both analogs had a lower affinity to VDR and that the stability of the induced VDR conformation, as measured by limited protease digestion assays, was similar (TX 527) or even weaker (TX 522) than that induced by the parent compound However, DNA-dependent assays such as gel shift expts. revealed that those analogs were slightly more potent (3-7 times) than 1,25(OH)2D3 in enhancing binding of VDR-RXR heterodimers to a direct repeat spaced by three nucleotides (DR3) type VDRE. The functional consequences of the ligand-VDR-RXR-VDRE interactions observed in vitro were subsequently evaluated in transfection expts. Both 14-epianalogs enhanced transcription of VDRE containing reporter constructs more efficiently than 1,25(OH)2D3 in COS-1 and MCF-7 cells regardless of the presence of ketoconazole. Transactivation activity is suggested to be a cell-specific process because maximal transcriptional induction and the half-maximal transactivation concentration for each reporter construct were different in both cell lines. The superagonistic transactivation activity closely resembled the biol. potency of these analogs on the inhibition of MCF-7 cell proliferation. These data clearly indicate that superagonistic activity starts beyond the binding of the ligand-heterodimer (VDR-RXR) complex to VDRE and thus probably involves coactivator/corepressor mols.

ST calcitriol epianalog vitamin D3 RXR receptor heterodimer VDRE element

IT Animal cell line
(COS-1; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity and cell selectivity)

IT Animal cell line
(MCF-7; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity and cell selectivity)

IT Transcriptional regulation
(activation; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT Cell differentiation
Proliferation inhibition
Transcriptional regulation
(calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT Vitamin D receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heterodimers with retinoid X receptors; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heterodimers with vitamin D3 receptors; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D-responsive element; calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

IT 32222-06-3D, 1,25-Dihydroxyvitamin D3, 14-epianalogs **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study);

PROC (Process)
(calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

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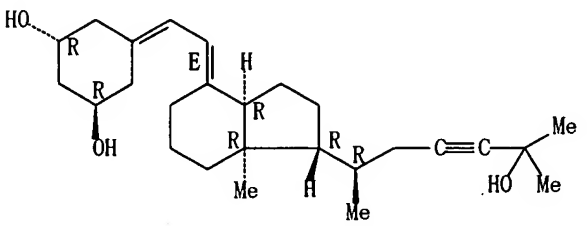
IT **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calcitriol epianalog interaction with vitamin D3 receptor-retinoid X receptor heterodimers on vitamin D3 responsive elements in relation to superagonistic activity)

RN 163217-09-2 HCAPLUS
CN 19-Nor-9, 10-secocholesta-5, 7-dien-23-yne-1, 3, 25-triol, (1α, 3β, 7E, 14β)- (9CI) (CA INDEX NAME)

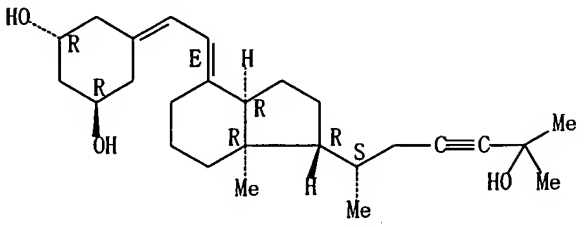
Absolute stereochemistry.
Double bond geometry as shown.



RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:414589 HCAPLUS
DN 133:276007
ED Entered STN: 22 Jun 2000
TI Analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants
AU Van Etten, Evelyne; Branisteanu, Dumitru D.; Verstuyf, Annemieke; Waer, Mark; Bouillon, Roger; Mathieu, Chantal
CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO) and Laboratory for Experimental Transplantation, Katholieke Universiteit Leuven, Louvain, 3000, Belg.
SO Transplantation (**2000**), 69(9), 1932-1942
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Background. Most immunosuppressants have a narrow margin between efficacy and side effects. A major goal in the development of immunomodulatory strategies is the discovery of combinations of drugs exerting synergistic immunomodulatory effects. The active form of vitamin D, 1,25(OH)2D3, is an immunomodulator that interacts with T cells but mainly targets antigen-presenting cells. We have demonstrated synergism between 1,25(OH)2D3 and cyclosporine, rapamycin, and FK506. The aim of this study was to investigate whether this synergism could be observed with other immunosuppressants (mycophenolate mofetil, leflunomide, and the methylxanthine A802715) and whether analogs of 1,25(OH)2D3 share this synergistic capacity in vivo. Methods. In vitro, the median effect anal. was applied to the inhibition of phytohemagglutinin A-induced lymphocyte proliferation. In vivo, synergism between analogs of 1,25(OH)2D3 and cyclosporine or mycophenolate mofetil was evaluated in exptl. autoimmune encephalomyelitis. Results. In vitro, all combinations with 1,25(OH)2D3 were synergistic. The strongest synergism was seen with the inhibitors of interleukin 2 secretion, cyclosporine and FK506 (indexes 0.16 and 0.27, resp.). The weakest synergism was observed in combinations using A802715, a second-signal inhibitor (index 0.52), or the nucleotide synthesis inhibitor mycophenolate mofetil (index 0.43). In vivo, analogs of 1,25(OH)2D3 share the in vitro-observed synergism with 1,25(OH)2D3. Moreover, the differences in synergism with different immunomodulators were also present in vivo, where the best synergism was again seen in combination with cyclosporine (up to 100% paralysis protection). Conclusions. These data confirm that 1,25(OH)2D3 and its analogs are potent dose-reducing drugs for other immunomodulators, making them potentially interesting for clin. use in autoimmunity and transplantation.
ST immunosuppressant dihydroxyvitamin D3 analog synergistic interaction
IT Immunosuppressants
(analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants)
IT Drug interactions
(synergistic; analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants)
IT 53123-88-9, Rapamycin 59865-13-3, Cyclosporin A 75706-12-6,

Leflunomide 104987-11-3, FK506 107767-58-8, A802715 128794-94-5, Mycophenolate mofetil
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants)

IT 32222-06-3D, 1,25-Dihydroxyvitamin D3, analogs 163216-79-3, ZG 1423 **163379-89-3**, TX 527 278184-44-4, WU 515
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants)

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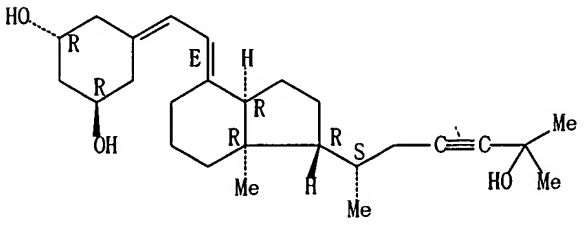
IT **163379-89-3**, TX 527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants)

RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:359365 HCAPLUS
DN 133:84708
ED Entered STN: 31 May 2000
TI Two novel 14-epi-analogues of 1,25-dihydroxyvitamin D3 inhibit the growth of human breast cancer cells in vitro and in vivo
AU Verlinden, Lieve; Verstuyf, Annemieke; Van Camp, Mark; Marcelis, Suzanne; Sabbe, Katrien; Zhao, Xu-Yang; De Clercq, Pierre; Vandewalle, Maurits; Bouillon, Roger
CS Laboratorium voor Experimentele Geneeskunde en Endocrinologie, Katholieke Universiteit Leuven, Louvain, 3000, Belg.
SO Cancer Research (**2000**), 60(10), 2673-2679
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The biol. activity of two novel 14-epi-analogs of 1,25(OH)2D3, 19-nor-14-epi-23-yne-1,25(OH)2D3 (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25(OH)2D3 (TX 527), is described. Both analogs were at least 10 times more potent than 1,25(OH)2D3 in inhibiting in vitro cell proliferation and had much lower in vivo calcemic effects than 1,25(OH)2D3. Treatment with 1,25(OH)2D3, TX 522, or TX 527 in vitro was accompanied by an accumulation of cells in the G1 phase of the cell cycle. Protein levels of cyclin C and cyclin D1 in in vitro cultures of MCF-7 cells were down-regulated to 50 and 30%, resp., of control levels at 72 and 120 h after stimulation. Protein levels of p21 and p27 at 72 h were significantly enhanced by 1,25(OH)2D3 and TX 522 but surprisingly not by TX 527. The inability of TX 527 to up-regulate p21 seemed to be cell type specific because p21 was induced in other cell types. Diminished phosphorylation of the retinoblastoma protein after treatment with 1,25(OH)2D3, TX 522, or TX 527 may ultimately contribute to the growth inhibition caused by these compds. According to the data presented, the induction of apoptosis seemed not to be a major mechanism responsible for the growth-inhibitory effect of 1,25(OH)2D3 and analogs. Both 14-epi-analogs significantly retarded tumor

progression (40% reduced compared with control mice) in an in vivo model of MCF-7 breast cancer cells established in nude mice. In conclusion, these novel analogs have the eligible profile to be tested as therapeutic agents for the treatment of hyperproliferative diseases such as breast cancer.

ST dihydroxyvitamin D3 analog TX522 antitumor breast; TX527 dihydroxyvitamin D3 analog antitumor breast

IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D1; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Interphase (cell cycle)
(G1-phase; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rb; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclins C; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene cdk4; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Antitumor agents
(mammary gland; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Mammary gland
Mammary gland
(neoplasm, inhibitors; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p15; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p19; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p27; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Phosphorylation, biological
(protein; two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Apoptosis
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Estrogen receptors
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT Vitamin D receptors
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT 32222-06-3, 1,25-Dihydroxyvitamin D3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT 32222-06-3D, 1,25-Dihydroxyvitamin D3, analogs **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

IT 7440-70-2, Calcium, biological studies 147014-97-9, CDK4 protein kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD

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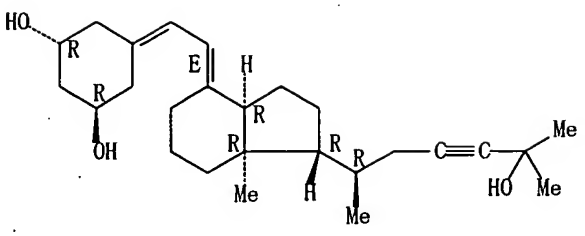
IT **163217-09-2**, TX 522 **163379-89-3**, TX 527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(two novel 14-epi-analogs of 1,25-dihydroxyvitamin D3 inhibit growth of human breast cancer cells in vitro and in vivo in mice)

RN 163217-09-2 HCAPLUS

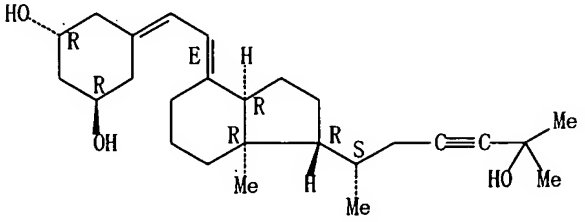
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:559556 HCAPLUS
DN 131:322829
ED Entered STN: 02 Sep 1999
TI Synthesis of 14,20-bis-epi-1α,25-dihydroxy-19-norvitamin D3 and analogs
AU Van Gool, Michiel; Zhao, Xu-Yang; Sabbe, Katrien; Vandewalle, Maurits
CS Dep. Organic Chemistry, Lab. Organic Synthesis, Univ. Gent, Ghent, B-9000, Belg.
SO European Journal of Organic Chemistry (**1999**), (9), 2241-2248
CODEN: EJOCFK; ISSN: 1434-193X
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
CC 32-7 (Steroids)
OS CASREACT 131:322829
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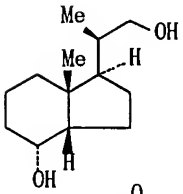

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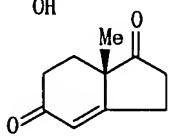

II

AB 14,20-Bis-epi-1α,25-dihydroxy-19-norvitamin D3 and side-chain analogs thereof were prepared via 14,20-bis-epi-Inhoffen-Lythgoe diol I. The synthesis of this precursor was performed via degradation of vitamin D2 and by total synthesis starting from Hajos-Wiechert ketone II.

ST norvitamin D3 prepn
IT Asymmetric synthesis and induction
(of hydroxynorvitamin D3 and analogs)
IT 50-14-6, Vitamin D2 17553-86-5 64190-52-9 174402-23-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of hydroxynorvitamin D3 and analogs)
IT 66774-80-9P 147352-03-2P 147352-04-3P 163216-62-4P 163216-63-5P
248257-31-0P 248257-34-3P 248257-36-5P 248257-37-6P 248257-39-8P
248257-40-1P 248257-41-2P 248257-42-3P 248257-43-4P 248257-46-7P
248257-47-8P 248257-48-9P 248257-49-0P 248257-50-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of hydroxynorvitamin D3 and analogs)
IT 124905-24-4P **163379-89-3P** 163379-90-6P 248257-32-1P
248257-33-2P 248257-35-4P 248257-38-7P 248257-44-5P 248257-45-6P
248257-51-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of hydroxynorvitamin D3 and analogs)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Barton, D; Chem Comm 1970, P939 HCAPLUS
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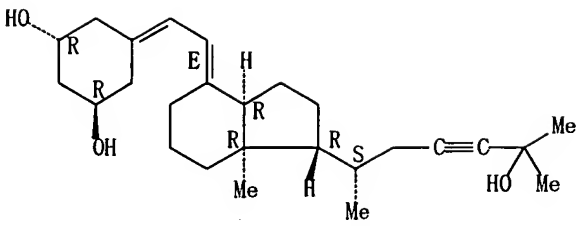
(33) Zhou, S; Tetrahedron Lett 1996, V37, P7637 HCAPLUS
(34) Zhu, G; Bioorg Med Chem Lett 1996, V6, P1703 HCAPLUS
IT **163379-89-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of hydroxynorvitamin D3 and analogs)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:761888 HCAPLUS
DN 130:20596
ED Entered STN: 04 Dec 1998
TI Cyclic ether vitamin D3 compounds, 1α-hydroxy-3-epivitamin D3 compounds and uses thereof
IN Reddy, Satayanarayana G.
PA Women & Infant's Hospital, USA
SO PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D309-06
ICS C07C401-00; A61K031-045
CC 1-12 (Pharmacology)
Section cross-reference(s): 2, 63
FAN.CNT 1

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PI	WO 9851678	A1	19981119	WO 1998-US10062	19980515 <--
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	US 6121312	A	20000919	US 1999-410223	19990930 <--
	US 6479538	B1	20021112	US 2000-617881	20000717 <--
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CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9851678	ICM	C07D309-06
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WO 9851678	ECLA	C07C401/00; C07D303/14; C07D307/32C; C07D309/04; C07D309/06 <--
US 6100294	NCL	514/451.000; 514/460.000; 549/416.000; 552/653.000
	ECLA	C07C401/00; C07D303/14; C07D307/32C; C07D309/04 <--
US 6121312	NCL	514/451.000; 514/460.000; 549/356.000; 549/416.000; 549/417.000; 549/428.000
	ECLA	C07C401/00; C07D303/14; C07D307/32C; C07D309/04; C07D309/06 <--
US 6479538	NCL	514/451.000; 424/562.000; 424/573.000; 424/577.000;

514/460.000; 549/423.000
ECLA C07C401/00; C07D303/14; C07D307/32C; C07D309/04; C07D309/06 <—
US 2003125309 NCL 514/167.000; 552/653.000; 549/416.000
ECLA C07C401/00; C07D303/14; C07D307/32C; C07D309/04; C07D309/06 <—

OS MARPAT 130:20596

AB Novel cyclic ether vitamin D3 compds. having a cyclic ether side chain are disclosed. These compds. were first identified as metabolites of 3-epivitamin D3 produced via a tissue-specific metabolic pathway which catalyzes the formation of a cyclic ether structure. Also disclosed are 1α-hydroxy-3-epivitamin D3 compds., which are produced via the epimerization of a 3-β-hydroxyl group of 1α-hydroxy-3-vitamin D3 precursor in vivo. The vitamin D3 compds. of the present invention can be used as substitutes for natural and synthetic vitamin D3 compds.

ST vitamin D3 cyclic ether therapeutics; skin hyperproliferative disorder vitamin D3 cyclic ether; endocrine disorder vitamin D3 cyclic ether; osteoporosis vitamin D3 cyclic ether; osteodystrophy vitamin D3 cyclic ether; hyperparathyroidism vitamin D3 cyclic ether; cirrhosis vitamin D3 cyclic ether; osteosarcoma vitamin D3 cyclic ether

IT Endocrine system
(disease; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Skin
(hyperproliferative disorders; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Bone, neoplasm
(osteosarcoma, inhibitors; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Bone, neoplasm
(osteosarcoma, vitamin D3 cyclic ether metabolism; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Antitumor agents
(osteosarcoma; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Bone, disease
Cirrhosis
Drug delivery systems
Hyperparathyroidism
(therapeutic activity of cyclic ether vitamin D3 compds.,)

IT Osteoporosis
(therapeutic agents; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT 7440-70-2, Calcium, biological studies 14265-44-2, Phosphate, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism; therapeutic activity of cyclic ether vitamin D3 compds.,)

IT 67-97-0 19356-17-3 32222-06-3 41294-56-8 42737-58-6 42737-59-7
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic activity of cyclic ether vitamin D3 compds.,)

IT 216246-78-5 216246-81-0 216246-82-1 216246-84-3 216246-85-4
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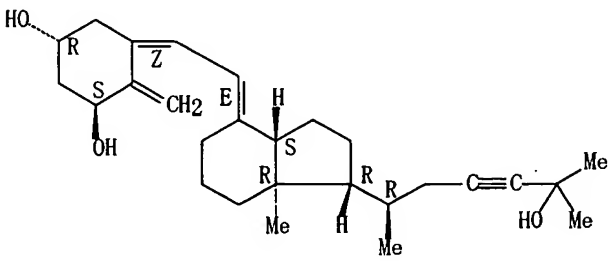
216383-29-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic activity of cyclic ether vitamin D3 compds.,)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Muralidharan, K; JOURNAL OF ORGANIC CHEMISTRY 1993, V58(7), P1895 HCAPLUS
(2) Okamura, W; JOURNAL OF ORGANIC CHEMISTRY 1978, V43(4), P574 HCAPLUS
(3) Scheddin, D; STEROIDS 1996, V61(10), P598 HCAPLUS

IT **119290-65-2 121664-09-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic activity of cyclic ether vitamin D3 compds.,)

RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

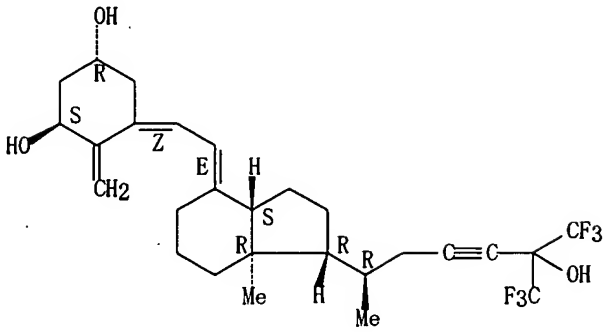
Absolute stereochemistry.
Double bond geometry as shown.



RN 121664-09-3 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, 26,26,26,27,27,27-hexafluoro-, (1α,3β,5Z,7E)- (9CI) (CA INDEX

NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:275234 HCAPLUS
DN 128:279055
ED Entered STN: 14 May 1998
TI Conformation-Function Relationship of Vitamin D: Conformational Analysis Predicts Potential Side-Chain Structure
AU Yamada, Sachiko; Yamamoto, Keiko; Masuno, Hiroyuki; Ohta, Masateru
CS Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, 101, Japan
SO Journal of Medicinal Chemistry (**1998**), 41(9), 1467-1475
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
CC 2-2 (Mammalian Hormones)
Section cross-reference(s): 22, 32
AB In previous studies, regions in space occupied by the vitamin D side chain were grouped into four: A, G, EA, and EG. The receptor (VDR) affinity of 1α,25-dihydroxyvitamin D3 derivs. increases, in terms of side-chain region, in the order EG, G, A, and EA. This was called the active space group concept. In the present study, this active space group concept was used to analyze the conformation-activity relationship of about 40 representative potent 1α,25-dihydroxyvitamin D3 analogs. Structural modifications in the side chain of potent vitamin D analogs were listed and estimated their potency factor. Possible side-chain conformations of representative analogs were calculated by the mol. mechanics method and plotted on a dot map compared with the regions A, G, EA, and EG. The cell-differentiating potency of the analogs was correlated with the active space group concept with few exceptions. Among potent analogs with a natural configuration at C(20), the side chains of those with a 22-oxa, 22-ene, 16-ene, or a 18-nor modification were located in front of region EA (termed F). The side chains of the most potent 20-epi-22-oxa-24-homovitamin D analogs were concentrated at the left side of the EA region (L-EA). Thus, the side chains of almost all potent analogs were distributed around the EA region, and potency increased in the order A, F, EA, and L-EA.
ST conformation vitamin D side chain structure
IT Conformation
Molecular mechanics
Structure-activity relationship
(conformation-function relationship of vitamin D, conformational anal. predicts potential side-chain structure)
IT Vitamin D receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conformation-function relationship of vitamin D, conformational anal. predicts potential side-chain structure)
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(conformation-function relationship of vitamin D, conformational anal. predicts potential side-chain structure)

RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD

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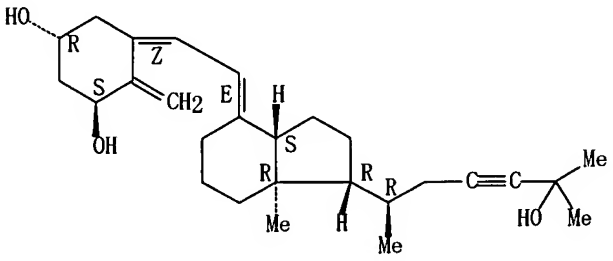
IT **119290-65-2 205673-01-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(conformation-function relationship of vitamin D, conformational anal. predicts potential side-chain structure)

RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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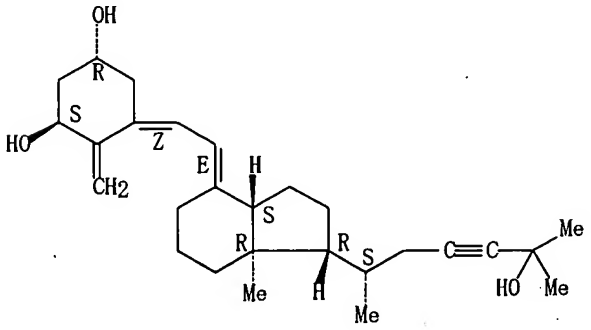
Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:18872 HCAPLUS
DN 124:45911
ED Entered STN: 09 Jan 1996
TI Growth inhibitory effects on human colon adenocarcinoma-derived Caco-2

cells and calcemic potential of 1α,25-dihydroxyvitamin D3 analogs: structure-function relationships

AU Bischof, M. G.; Redlich, K.; Schiller, C.; Chirayath, M. V.; Uskokovic, M.; Peterlik, M.; Cross, H. S.

CS Department of General and Experimental Pathology, University of Vienna Medical School, Vienna, Austria

SO Journal of Pharmacology and Experimental Therapeutics (**1995**), 275(3), 1254-60
CODEN: JPETAB; ISSN: 0022-3565

PB Williams & Wilkins

DT Journal

LA English

CC 2-2 (Mammalian Hormones)

AB A panel of synthetic analogs of 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3] bearing one or multiple structural modifications at functionally or metabolically sensitive positions of the mol., i.e., C-1, 16, 23, 26 and 27, were tested for their growth inhibitory and prodifferentiating potency in human colon adenocarcinoma-derived Caco-2 cells. With respect to the peak response elicited at 10-8 M, 1α,25-dihydroxy-16-ene-vitamin-D3, 1α,25-dihydroxy-23-yne-vitamin D3 and 1α,25-dihydroxy-16,23Z-diene-vitamin D3 suppressed [3H]thymidine incorporation in confluent Caco-2 cells less than 1α,25(OH)2D3. 1α,25-Dihydroxy-16,23E-diene-vitamin D3 was at least equipotent to the parent compound, whereas 1α,25-dihydroxy-16-ene-23-yne-vitamin D3 and most conspicuously 1α,25-dihydroxy-26,27-hexafluoro-16-ene-23-yne-vitamin D3 reduced growth of Caco-2 cells to significantly lower levels than 1α,25(OH)2D3. The same rank order was obtained for the ability of the vitamin D compds. to induce activity of the differentiation marker enzyme, alkaline phosphatase, in quiescent Caco-2 cells. Whereas the effect of the synthetic analogs on calcium uptake by cultured embryonic chick duodenum in general was less pronounced than that of 1α,25(OH)2D3, the two most potent antimitogenic compds., 1α,25(OH)2D3, the two most potent antimitogenic compds., 1α,25-dihydroxy-16-ene-23-yne-vitamin D3 and 1α,25-dihydroxy-26,27-hexafluoro-16-ene-23-yne-vitamin D3, elicited calcium mobilization from cultured neonatal mouse calvaria at a 10-fold lower concentration than the parent compound In addition, these two synthetic analogs also were potent inducers of osteoclast-like cell differentiation in mouse bone marrow cultures, so that in vivo a hypercalcemic effect of these vitamin D compds. at effective growth ID levels must be considered possible. In contrast, 1α,25-dihydroxy-16,23E-diene-vitamin D3 matches if not exceeds 1α,25(OH)2D3 in its antiproliferative and prodifferentiating efficacy in neoplastic colonic epithelial cells, but is a less potent inducer or intestinal calcium transport and bone calcium mobilization.

ST colon adenocarcinoma dihydroxyvitamin D3 analog; calcium mobilization bone intestine dihydroxyvitamin D3; Caco2 cell growth dihydroxyvitamin D3 analog

IT Resorption
(bone; dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Biological transport
Bone
Cell proliferation
(dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Cell differentiation
Osteoclast
(dihydroxyvitamin D3 analogs effect on osteoclast differentiation in relation to structure)

IT Animal cell line
(Caco-2, dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Molecular structure-biological activity relationship
(antimitotic, dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Molecular structure-biological activity relationship

(calcium-mobilizing, dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Intestine, neoplasm
(colon, adenocarcinoma, dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT Intestine
(duodenum, dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT 32222-06-3, 1α,25-Dihydroxyvitamin D3 **119290-65-2**
124409-57-0 124409-58-1 124409-59-2 124409-60-5 137102-93-3
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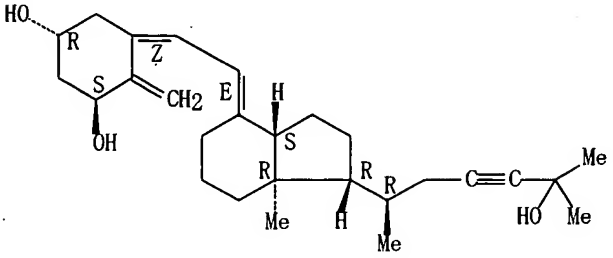
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

IT **119290-65-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(dihydroxyvitamin D3 analogs antimitogenic effects in Caco-2 cells and calcium mobilizing effects in bone and intestine in relation to structure)

RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:563269 HCAPLUS
DN 122:314933
ED Entered STN: 23 May 1995
TI Novel structural analogs of vitamin D
IN Bouillon, Roger; Vandewalle, Maurits; de Clercq, Pierre Jean
PA Laboratoire Theramex S.A., Monaco
SO PCT Int. Appl., 192 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C401-00
ICS A61K031-59; C07C049-523; C07C035-27; C07C047-347; C07C069-757
CC 32-7 (Steroids)
Section cross-reference(s): 1, 2, 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9501960	A1	19950119	WO 1994-EP2294	19940707 <--

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CLASS
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                         C07C059/01; C07C401/00; C07C035/27; C07C047/192;
                         C07C047/198; C07C047/36; C07C047/37; C07C049/242;
                         C07C049/517; C07C049/687                          <--
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                         C07C401/00                                        <--
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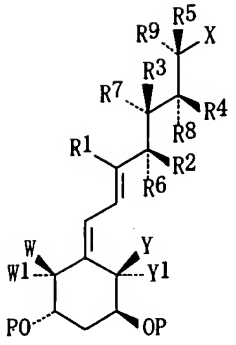

I

AB The invention relates to analogs of vitamin D, which lack the combined presence of the trans-fused six-membered C-ring and of five-membered D-ring, but still possess a central part consisting of a substituted chain of five atoms, atoms which correspond to positions 8, 14, 13, 17 and 20 of vitamin D, and at the ends of which are connected, at position 20 a structural moiety representing part of the side-chain of vitamin D or of an analog of vitamind D, and at position 8 the Δ(5,7)-diene moiety connected to the a-ring of the active 1-alpha-hydroxy metabolite or of an established vitamin D analog, represented by I (P = H, alkyl, acyl; Y and Y1, X and X1 = H, alkyl, when taken together represent an alkylidene group or form a carbocyclic ring; R-R9 may form an unsatd. carbocyclic or heterocyclic ring when located in a relative 1,3-position, 1,2-position, and a 1,1-position along the central chain) to their preparation process, to preparation intermediates, to pharmaceutical prepns. comprising these compds. and to their use in medicine.

ST vitamin D analog

IT Immunosuppressants
Inflammation inhibitors
Neoplasm inhibitors
Skin
(preparation of structural analogs of vitamin D)

IT Receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(vitamin D, preparation of structural analogs of vitamin D)

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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of structural analogs of vitamin D)

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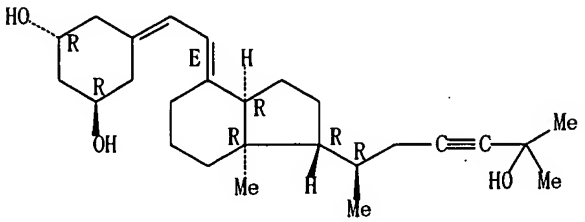
163216-50-0P 163216-51-1P 163216-52-2P 163216-53-3P 163216-54-4P
163216-55-5P 163216-56-6P 163216-57-7P 163216-58-8P 163216-59-9P
163216-61-3P 163216-62-4P 163216-63-5P 163216-65-7P 163216-66-8P
163216-67-9P 163216-68-0P 163216-69-1P 163216-73-7P 163216-76-0P
163216-81-7P 163216-84-0P 163217-17-2P 163217-18-3P 163217-19-4P
163217-20-7P 163217-21-8P 163217-22-9P 163217-23-0P 163217-24-1P
163217-25-2P 163217-26-3P 163217-27-4P 163217-28-5P 163217-29-6P
163217-30-9P 163217-31-0P 163217-33-2P 163217-34-3P 163379-46-2P
163379-47-3P 163379-48-4P 163379-49-5P 163379-50-8P 163379-51-9P
163379-52-0P 163379-53-1P 163379-54-2P 163379-55-3P 163379-56-4P
163379-57-5P 163379-58-6P 163379-59-7P 163379-60-0P 163379-61-1P
163379-62-2P 163379-63-3P 163379-64-4P 163379-65-5P 163379-66-6P
163379-67-7P 163379-68-8P 163379-69-9P 163379-70-2P 163379-71-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of structural analogs of vitamin D)

IT 77-95-2, (-)-Quinic acid 14073-97-3, (-)-Menthone 18890-22-7 18951-85-4, (R)-(+)-Citronellic acid 26543-05-5 39807-00-6 66774-80-9 70550-73-1 81522-68-1 119478-74-9 139356-39-1 163216-64-6 163217-32-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of structural analogs of vitamin D)

IT **163217-09-2P 163217-11-6P 163379-89-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of structural analogs of vitamin D)

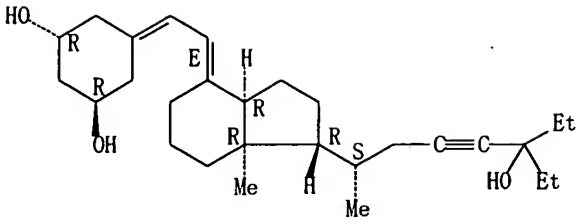
RN 163217-09-2 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



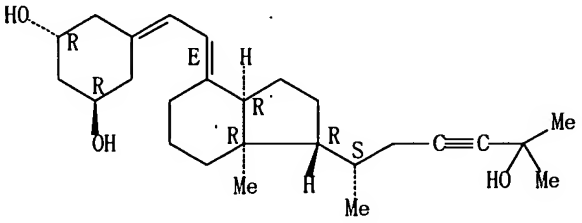
RN 163217-11-6 HCAPLUS
CN 1,3-Cyclohexanediol, 5-[[1-(5-ethyl-5-hydroxy-1-methyl-3-heptynyl)octahydro-7a-methyl-4H-inden-4-ylidene]ethylidene]-, [1R-[1α(S*),3aα,4E(1R*,3R*),7aα]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:523549 HCAPLUS
DN 122:282993
ED Entered STN: 04 May 1995
TI Potent vitamin D3 analogs: their abilities to enhance transactivation and to bind to the vitamin D3 response element
AU Imai, Yasufumi; Pike, J. Wesley; Koeffler, H. Phillip
CS School of Medicine, UCLA, Los Angeles, CA, 90043, USA
SO Leukemia Research (**1995**), 19(3), 147-58
CODEN: LEREDD; ISSN: 0145-2126
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 18
AB 1,25 Dihydroxyvitamin D3 [1,25(OH)2D3] mediates its biol. activities through specific binding to the vitamin D3 receptor (VDR) and subsequent association with vitamin D3 responsive elements (VDRE) in genes modulated by 1,25(OH)2D3. Several novel vitamin D3 compds. (Cmpds) have recently been identified which have 5- to 1000-fold greater abilities to induce differentiation and to inhibit proliferation of HL-60 leukemic blast cells as compared to the parental 1,25(OH)2D3 (code name, Cmpd C). To clarify the mechanism by which five of these vitamin D3 analogs [1,25(OH)2-16ene-D3, (Cmpd HM); 1,25(OH)2-16ene-23yne-D3, (Cmpd V); 1,25(OH)2-16ene-23yne-26,27 F6-D3; 22-Oxa-1,25(OH)2D3; 1,25(OH)2-23yne-D3] mediate their remarkably potent biol. activities, the authors have investigated their abilities in HL-60 cells to transactivate a chloramphenicol acetyl transferase (CAT) reporter gene containing a VDRE from the human osteocalcin gene attached to a thymidine kinase minimal promoter. Also, the abilities of the analogs to enhance the binding of the human recombinant VDR/retinoic X receptorα (RXRα) heterodimer to the VDRE were examined in gel mobility shift assays. In serumless cultures, a series of potent vitamin D3 analogs had comparable abilities to transactivate the reporter gene as did the biol. less potent 1,25(OH)2D3 (≈ 15-20-fold stimulation in cultures containing 2+10-8M of vitamin D3 compds). Biol. very weak inducers of differentiation of HL-60 [24R,25(OH)2D3; 25(OH)-16ene-23yne-D3] had markedly diminished abilities to induce transactivation. Dose-response studies of Cmpds C, V, HM (10-7-10-11M) showed that in serumless culture conditions, transactivation of the VDRE-CAT was similar; however, in the

presence of serum, Cmpd C at 10-9M had 20-fold less activity than analogs V and HM. These results may reflect increased binding of Cmpd C to the D binding protein (DBP) in serum as compared to the lower binding affinities for DBP by Cmpds HM and V. Affinities of the biol. potent analogs for VDR did not parallel their abilities either to transactivate VDRE-CAT or to mediate a biol. affect on HL-60 cells. In further studies, gel mobility shift assays showed that VDR alone did not have detectable binding to VDRE; likewise, VDR plus RXR had little binding to VDRE in the absence of ligand. In contrast, biol. active vitamin D3 compds. (Cmpds HM, C, V) in a dose-dependent fashion enhanced the VDR/RXR (retinoid X receptor)-VDRE retarded band. Cmpds HM and C(10-9-10-7M) produced a greater enhancement of the retarded band than did Cmpd V, perhaps reflecting the lower binding affinity of the latter Cmpd for VDR. In summary, the transactivational studies suggest that the differential potencies of the new vitamin D3 analogs may relate in part to their binding affinities to DBP. This is unlikely to be the entire explanation because the authors find a lack of parallelism between the rank order of the potent vitamin D3 analogs to mediate their biol. activities and their abilities to bind VDR, to transactivate a VDRE and to enhance the magnitude of the VDR/RXR-VDRE retarded band. Further studies should focus on differential metabolism of the analogs as well as potential differences in conformational changes of the VDR/RXR when bound to the vitamin D3 ligands.

ST vitamin D3 analog transactivation response element

IT Blood serum
Cell differentiation
Cell proliferation
(vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

IT Retinoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXRα (retinoic acid receptor X α), vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXRα (retinoid X receptor α), vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D-binding, vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D-responsive element, vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

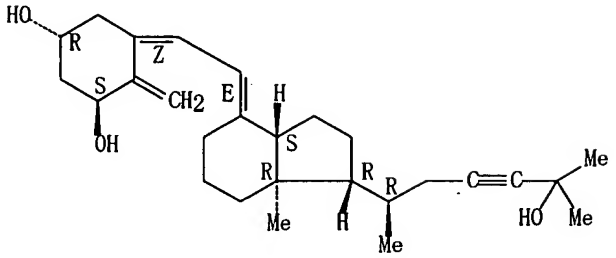
IT 67-97-0D, Vitamin D3, analogs 32222-06-3, 1,25-Dihydroxyvitamin D3 103909-75-7, 22-Oxa-1,25-dihydroxy-vitamin D3 118694-43-2 **119290-65-2** 124409-58-1 137102-93-3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

IT **119290-65-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vitamin D3 analogs enhancement of transactivation and binding by vitamin D3 response element in HL-60 leukemic blast cells)

RN 119290-65-2 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

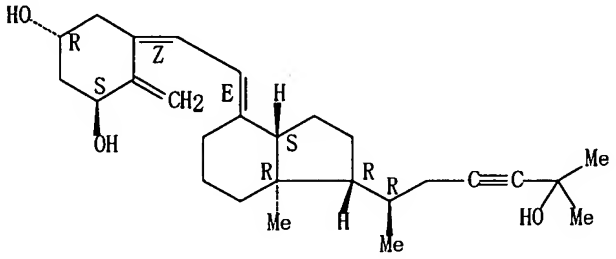
Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:292389 HCAPLUS
DN 122:72583
ED Entered STN: 12 Jan 1995
TI Monocytic differentiation of HL60 cells induced by potent analogs of vitamin D3 precedes the G1/G0 phase cell cycle block
AU Zhang, F.; Godyn, J. J.; Uskokovic, M.; Binderup, L.; Studzinski, G. P.
CS Department Laboratory Medicine and Pathology, UMDNJ- New Jersey Medical School, Newark, NJ, 07103-2714, USA
SO Cell Proliferation (**1994**), 27(11), 643-54
CODEN: CPROEM; ISSN: 0960-7722
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 1
AB Differentiation of mammalian cells is accompanied by reduced rates of proliferation and an exit from the cell cycle. Human leukemic cells HL60 present a widely used model of neoplastic cell differentiation, and acquire the monocytic phenotype when exposed to analogs of vitamin D3 (VD3). The maturation process is accompanied by two blocks in the cell cycle: an arrest in the G1/G0 phase, and a recently described G2 + M block. In this study the authors have analyzed the traverse of the cell cycle phases of the well-differentiating HL60-G cells exposed to one of ten analogs of VD3, and compared the cell cycle effects of each compound with its potency as a differentiation-inducing agent. The authors found that in general there was a good correlation between the effects of these compds. on the cell cycle and on differentiation, but the best cell cycle predictor of differentiation potency was the extent of accumulation of the cells in the G2 compartment. All analogs induced a marked decrease in the mitotic index, and polynucleation of HL60 cells was produced, especially by compds. which were effective as inducers of differentiation. Time course studies showed that induction of differentiation was accompanied by a transient increase of the proportion of cells in the G2 + M compartment, but preceded the G1 to S, and the G2 compartment blocks. These studies indicate that complex changes in the cell cycle traverse accompany, but do not precede, the acquisition of the monocytic phenotype by HL60 cells.
ST leukemia monocyte differentiation vitamin D
IT Cell cycle
Cell differentiation
Cell proliferation
Interphase, biological
Leukemia
Mitosis
Neoplasm inhibitors
(monocytic differentiation of human leukemic cells in response to vitamin D3 analogs in relation to cell cycle)
IT 67-97-0D, Vitamin D3, analogs 32222-06-3, 1,25-Dihydroxyvitamin D3 103909-75-7, 22-Oxa-calcitriol 118694-43-2 **119290-65-2** 124409-58-1 124409-59-2 131875-08-6, KH 1060 134404-52-7, EB 1089 134523-84-5, MC 1288 137102-93-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monocytic differentiation of human leukemic cells in response to vitamin D3 analogs in relation to cell cycle)
IT **119290-65-2**

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monocytic differentiation of human leukemic cells in response to vitamin D3 analogs in relation to cell cycle)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

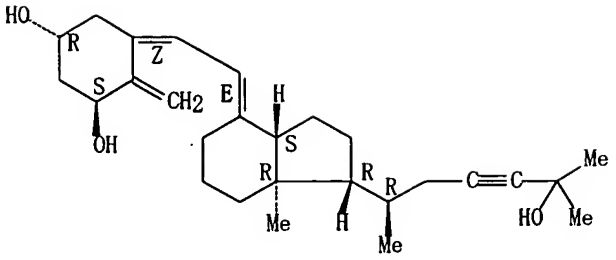
Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:76909 HCAPLUS
DN 122:46683
ED Entered STN: 08 Nov 1994
TI Profile of ligand specificity of the vitamin D binding protein for 1α,25-dihydroxyvitamin D3 and its analogs
AU Bishop, June E.; Collins, Elaine D.; Okamura, William H.; Norman, Anthony W.
CS Department Biochemistry, University California, Riverside, CA, USA
SO Journal of Bone and Mineral Research (**1994**), 9(8), 1277-88
CODEN: JBMREJ; ISSN: 0884-0431
DT Journal
LA English
CC 2-2 (Mammalian Hormones)
AB The profile of structural preference for the ligand binding domain of the human vitamin D binding protein (DBP) was determined by steroid competition assay of 71 analogs of 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3]. The following categories of structural modification were evaluated [values represent fold change; R = reduction, I = increase in binding to the DBP from the reference 1α,25(OH)2D3]: (1) deletion in the A ring of the 1α-hydroxyl (20-1600I); (2) conversion of the triene system to the previtamin form (6-40R); (3) addition of substituents to carbon 11 of the C ring (4-14R); (4) inversion of the C/D ring junction (8-20R); (5) unsatn. of the D ring (16-ene; 4-140R); (6) replacement of hydrogen with deuterium atoms (no effect); alteration of the side chain by (7) adding or deleting carbon atoms (5-12R); (8) addition of fluorines (0.2-10R); (9) presence of unsatn. (22-ene, 0-5R; 23-ene, 3R-10I; 23-yne, 5-20R); (10) addition of hydroxyls (2-100R); and (11) addition of an aromatic ring (0-20I). Thus, the DBP ligand binding domain could tolerate only modest changes to the structure of 1α,25(OH)2D3 without a reduction in binding of the analog. The increases in binding seen in the aromatic side chain and with a triple bond at carbon-23 may be indicative of a preferred conformation of the flexible 1α,25(OH)2D3 side chain. In addition, a comparison was made of the DBP ligand binding domain with that of the human HL-60 cell 1α,25(OH)2D3 nuclear receptor. Both ligand binding domains could equivalently accommodate to the presence of (1) a side-chain cyclopropyl group, (2) 22-ene or 23-yne, (3) lengthening the side chain by two carbons, (4) presence of four to six fluorine atoms, (5) substitution of an oxygen for carbon 22, and (6) presence of a 22-[m-(dimethylhydroxymethyl)phenyl] aromatic group in the side chain. The DPB could tolerate better than the HL-60 cell receptor the presence of a 22-(p-hydroxyphenyl) aromatic group in the side chain and the absence of the 1α-hydroxyl. In contrast, the HL-60 cell receptor could tolerate better than the DBP the following structural modifications: presence of a 16-ene, or 16-ene plus 23-yne unsatn., and presence of an 11β-hydroxyl.
ST vitamin D binding protein binding domain; dihydroxyvitamin D3 analog

binding DBP
IT Molecular structure-biological activity relationship
(vitamin D-binding protein-binding; of 1α,25-dihydroxyvitamin D3 analogs)
IT Globulins, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gc, ligand specificity of human vitamin D binding protein for 1α,25-dihydroxyvitamin D3 and analogs)
IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3, ligand specificity of human nuclear vitamin D3 receptor for 1α,25-dihydroxyvitamin D3 and analogs)
IT Molecular structure-biological activity relationship
(dihydroxyvitamin D3 receptor-binding, of 1α,25-dihydroxyvitamin D3 analogs)
IT 67-97-0, Vitamin D3 128-27-8, Pyrocalciferol 434-16-2, 7-Dehydrocholesterol 474-70-4, Isopyrocalciferol 5226-01-7, Lumisterol-3 7439-89-6D, Iron, complexes with vitamin D3 derivs. 7440-48-4D, Cobalt, complexes with vitamin D3 derivs. 19356-17-3D, 25-Hydroxyvitamin D3, iron complexes 22145-68-2, 25-Hydroxy-7-dehydrocholesterol 36149-00-5D, 25-Hydroxy-5,6-trans-vitamin D3, iron complexes 42737-59-7 55721-11-4, 24R,25-Dihydroxyvitamin D3 56142-94-0 61476-45-7 61585-29-3, 25-Hydroxylumisterol-3 61954-91-4, 1α,25-Dihydroxy-7-dehydrocholesterol 65120-25-4, 24-Nor-1α,25-dihydroxyvitamin D3 66791-71-7, 1β,25-Dihydroxyvitamin D3 77372-59-9 77647-50-8 80463-19-0 86701-33-9 96614-28-7 114906-52-4 119290-66-3 120244-55-5 121664-10-6 124409-57-0 124409-59-2 137548-45-9 140387-46-8 142700-19-4 142700-20-7 157380-24-0, 14-epi-25-Hydroxyvitamin D3 157380-25-1, 14-epi-1α,25-Dihydroxyvitamin D3 157380-26-2, 14-epi-25-Hydroxy-pre-vitamin D3 157380-27-3, 14-epi-1α,25-Dihydroxy-pre-vitamin D3 157469-26-6 158398-88-0 158398-90-4 158398-91-5D, cobalt complexes 158398-92-6 158513-10-1 158513-11-2 159910-53-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ligand specificity for human vitamin D-binding protein)
IT 19356-17-3, 25-Hydroxyvitamin D3 41294-56-8, 1α-Hydroxyvitamin D3 60133-18-8, 1α,25-Dihydroxyvitamin D2 83805-11-2 91874-90-7 101558-90-1 103420-55-9 103656-40-2 103909-75-7, 22-Oxa-1α,25-dihydroxyvitamin D3 104870-37-3 112965-21-6 114694-09-6 118694-43-2 **119290-65-2** 124409-58-1 124409-60-5 124409-61-6 133910-08-4 133910-09-5 133910-11-9 137102-93-3 137102-94-4 137102-95-5 158398-89-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ligand specificity for human vitamin D-binding protein and human nuclear vitamin D3 receptor)
IT 32222-06-3, 1α,25-Dihydroxyvitamin D3
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(ligand specificity of human nuclear vitamin D3 receptor for 1α,25-dihydroxyvitamin D3 and analogs)
IT **119290-65-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ligand specificity for human vitamin D-binding protein and human nuclear vitamin D3 receptor)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

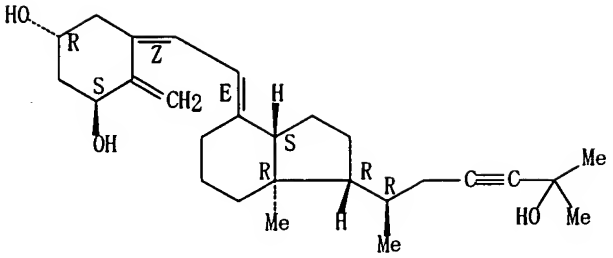
Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:237443 HCAPLUS
DN 120:237443
ED Entered STN: 14 May 1994
TI Highly potent transcriptional activation by 16-ene derivatives of 1,25-dihydroxyvitamin D3. Lack of modulation by 9-cis-retinoic acid of response to 1,25-dihydroxyvitamin D3 or its derivatives
AU Ferrara, John; McCuaig, Kimberly; Hendy, Geoffrey N.; Uskokovic, Milan; White, John H.
CS Dep. Physiol., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SO Journal of Biological Chemistry (**1994**), 269(4), 2971-81
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 13
AB Although several studies have been performed on the biol. activities of analogs of 1,25-dihydroxyvitamin D3 (1,25-(OH)2 D3) at the whole animal and cellular levels, little work has been done to analyze their transcriptional activation properties. A highly inducible 1,25-(OH)2 D3-responsive promoter composed of three copies of the mouse osteopontin vitamin D3 response element (VDRE3) inserted upstream of a herpes simplex virus thymidine kinase promoter has been constructed, and its transcriptional properties have been analyzed by transient transfection into the monkey kidney cell line COS-7 and the rat osteoblast-like osteosarcoma line ROS 17/2.8. The authors have studied systematically transcriptional activation by a number of 1,25-(OH)2 D3 analogs, particularly those substituted at positions 16, 23, 26, and 27, sites that are targets for metabolism Strikingly, except for derivs. that bind the 1,25-(OH)2 D3 receptor (VDR) very weakly, the authors find no parallel between the potency of action of a derivative as a transcriptional inducer and its affinity for the VDR. Derivs. substituted by multiple bonds at positions 16 and/or 23, although having varying affinities for the VDR, all stimulate transcription more potently than D3, in some cases at 100-fold lower concns. The peak transcriptional activity observed varies by only approx. 20% among different active analogs, indicating little difference in the activity of the VDR once bound to ligand. Gel retardation assays with ROS 17/2.8 nuclear exts. suggest that the VDR binds to the mouse osteopontin VDRE predominantly as a heterodimer with retinoid X receptor(s) (RXR(s)). The authors find that 9-cis-retinoic acid, the cognate ligand for RXRs, does not have a significant effect on the response of the VDRE3 promoter to 1,25-(OH)2 D3 or a number of its derivs. in ROS 17/2.8 or in COS-7 cells, under conditions in which promoters containing retinoid X response elements are activated. This suggests that 9-cis-retinoic acid may not act on the response to 1,25-(OH)2 D3 or its derivs. by directly influencing the transcriptional activity of VDR/RXR heterodimers. This promoter/reporter system should be useful for analyzing the tissue-specific transcriptional activity of 1,25-(OH)2 D3 and its derivs. in any cell type amenable to transient transfection.
ST dihydroxyvitamin D3 deriv transcription activation; mouse osteopontin vitamin D3 response element; retinoate transcription activation dihydroxyvitamin D3; retinoid X dihydroxyvitamin D3 receptor heterodimer; promoter reporter system transcription dihydroxyvitamin D3
IT Gene, animal
RL: BIOL (Biological study)
(for osteopontin, vitamin D3 response element of mouse, transcriptional

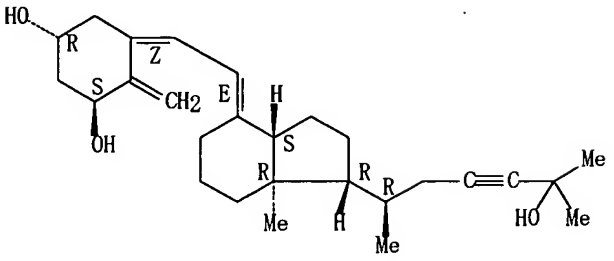
activation by dihydroxyvitamin D3 derivs. of promoter construct containing)
IT Transcription, genetic
(from mouse osteopontin vitamin D3 response element-containing promoter construct, by dihydroxyvitamin D3 derivs., lack of modulation by retinoic acid of)
IT Mouse
(osteopontin gene vitamin D3 response element of, transcriptional activation by dihydroxyvitamin D3 derivs. of promoter construct containing)
IT Molecular structure-biological activity relationship
(transcription-activating, of dihydroxyvitamin D3 derivs., assayed with mouse osteopontin vitamin D3 response element-containing promoter construct)
IT Genetic element
RL: BIOL (Biological study)
(vitamin D3 response element, from mouse osteopontin gene, transcriptional activation by dihydroxyvitamin D3 derivs. of promoter construct containing)
IT Animal cell line
(COS-7, monkey kidney, transcription activation by dihydroxyvitamin D3 derivs. of mouse osteopontin vitamin D3 response element-containing promoter construct in)
IT Animal cell line
(ROS 17/2.8, rat osteosarcoma, transcription activation by dihydroxyvitamin D3 derivs. of mouse osteopontin vitamin D3 response element-containing promoter construct in)
IT Receptors
RL: BIOL (Biological study)
(RXRα (retinoid X receptor α), mouse osteopontin vitamin D3 response element promoter construct binding by dihydroxyvitamin D3 heterodimer with)
IT Retinoids
RL: BIOL (Biological study)
(RXRα receptors, mouse osteopontin vitamin D3 response element promoter construct binding by dihydroxyvitamin D3 heterodimer with)
IT Receptors
RL: BIOL (Biological study)
(dihydroxyvitamin D3, mouse osteopontin vitamin D3 response element promoter construct binding by retinoid X receptor α heterodimer with)
IT Glycophosphoproteins
RL: BIOL (Biological study)
(osteopontins, gene for mouse, vitamin D3 response element of, transcriptional activation by dihydroxyvitamin D3 derivs. of promoter construct containing)
IT 5300-03-8, 9-cis-Retinoic acid
RL: BIOL (Biological study)
(transcriptional activation by dihydroxyvitamin D3 and derivs. in relation to)
IT 32222-06-3 32222-06-3D, derivs. 55721-11-4 118694-43-2
119290-65-2 124409-57-0 124409-58-1 124409-59-2
137102-93-3 137102-95-5 154196-92-6 154279-14-8
RL: BIOL (Biological study)
(transcriptional activation of vitamin D3 response element-containing promoter construct by, lack of modulation by retinoic acid of)
IT **119290-65-2**
RL: BIOL (Biological study)
(transcriptional activation of vitamin D3 response element-containing promoter construct by, lack of modulation by retinoic acid of)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:124319 HCAPLUS
DN 120:124319
ED Entered STN: 19 Mar 1994
TI Interaction of retinoic acid and vitamin D3 analogs on HL-60 myeloid leukemic cells
AU Dore, Benoit T.; Uskokovic, Milan R.; Momparler, Richard L.
CS Dep. pharmacol., Univ. Montreal, Montreal, QC, H3T 1C5, Can.
SO Leukemia Research (**1993**), 17(9), 749-57
CODEN: LEREDD; ISSN: 0145-2126
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Retinoic acid (RA) is an interesting agent which has been shown to induce differentiation and complete remission in patients with acute promyelocytic leukemia. 1,25-(OH)2-Δ16-23-yne-cholecalciferol (16-23 Da3) and 1,25-(OH)2-23-yne-cholecalciferol (23 Da3) are vitamin D3 analogs capable of inducing differentiation of myeloid leukemic cells with little effect on either calcium absorption or mobilization. Using HL-60 myeloid leukemic cells as an in vitro model for human acute myeloid leukemia, the authors observed an additive to synergistic interaction between RA and 16-23 Da3 or 23 Da3 with respect to the inhibition of cell growth and DNA synthesis, the induction of differentiation and the loss of cell clonogenicity. In addition, the authors observed that RA and 16-23 Da3 interact additively with respect to the reduction of c-myc mRNA expression. These results suggest that RA used in combination with 16-23 Da3 or 23 Da3 may be an interesting chemotherapeutic regimen to evaluate in patients with acute myeloid leukemia.
ST retinoate vitamin D3 analog leukemia inhibitor; c myc gene retinoate vitamin D3
IT Drug interactions
(of retinoic acid and vitamin D3 analogs, in myeloid leukemia of humans inhibition, c-myc gene expression in)
IT Gene, animal
RL: BIOL (Biological study)
(c-myc, expression of, retinoic acid and vitamin D3 analogs effect on, in myeloid leukemia of humans inhibition)
IT Neoplasm inhibitors
(myelogenous leukemia, retinoic acid and vitamin D3 analogs as, interaction in, c-myc gene expression in, in human cells)
IT 118694-43-2 **119290-65-2**
RL: BIOL (Biological study)
(myeloid leukemia of humans inhibition by, retinoic acid enhancement of, c-myc gene expression in)
IT 302-79-4, All trans-retinoic acid
RL: BIOL (Biological study)
(myeloid leukemia of humans inhibition by, vitamin D3 analogs enhancement of, c-myc gene expression in)
IT **119290-65-2**
RL: BIOL (Biological study)
(myeloid leukemia of humans inhibition by, retinoic acid enhancement of, c-myc gene expression in)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

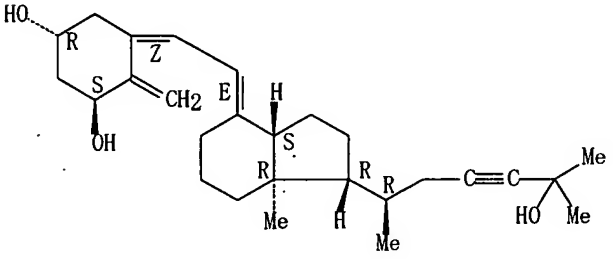
Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:95686 HCAPLUS
DN 120:95686
ED Entered STN: 05 Mar 1994
TI Regulation of keratinocyte growth, differentiation, and vitamin D metabolism by analogs of 1,25-dihydroxyvitamin D
AU Bikle, Daniel D.; Gee, Elaine; Pillai, Sreekumar
CS Dep. Med., Univ. California, San Francisco, CA, USA
SO Journal of Investigative Dermatology (**1993**), 101(5), 713-18
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 2
AB 1,25-Dihydroxyvitamine D (1,25(OH)2D) has numerous actions on many tissues. Analogs of 1,25(OH)2D are being sought that are selective, to further an understanding of the mechanisms of action of 1,25(OH)2D and to improve its therapeutic efficacy. Toward these ends the authors examined eight analogs of 1,25(OH)2D for their ability to regulate 25-hydroxyvitamin D (25OHD) metabolism by keratinocytes. Choosing the three most potent, the authors then examined their ability to inhibit keratinocyte proliferation, stimulate cornified envelope formation (a marker of differentiation), and bind to the 1,25(OH)2D receptor (VDR). 1,25(OH)2-24F2D, 1,25(OH)2-Δ16-D, and 1,25(OH)2-Δ16,23yne-D proved the most potent in inhibiting 1,25(OH)2D production and stimulating 24,25(OH)2D production, being approx. 10-100 times more potent than 1,25(OH)2D itself. 1,25(OH)2-Δ16-D had the highest affinity for the VDR (fourfold higher than that for 1,25(OH)2D itself) and had the greatest ability both to inhibit proliferation and to stimulate differentiation. 1,25(OH)2-Δ16,23yne-D also had a higher affinity for the VDR, but was of less or equal potency in stimulating cornified envelope formation and inhibiting proliferation. 1,25(OH)2-24F2-D, which was the most potent regulator of 25OHD metabolism, had a lower affinity for the VDR and was less potent than 1,25(OH)2D in inhibiting proliferation. The authors' results indicate that even in the same cell, different analogs have different rank orders of potency for the various actions of 1,25(OH)2D.
ST keratinocyte growth differentiation hydroxyvitamin D analog
IT Cell differentiation
Cell proliferation
(by keratinocytes of humans, dihydroxyvitamin D analogs stimulation of, structure in relation to)
IT Molecular structure-biological activity relationship
(keratinocytes differentiation and proliferation-affecting, of dihydroxyvitamin D analogs, in human cells)
IT Receptors
RL: BIOL (Biological study)
(dihydroxyvitamin D3, dihydroxyvitamin D analogs binding to, in keratinocytes of humans, structure in relation to)
IT Molecular structure-biological activity relationship
(dihydroxyvitamin D3 receptor-binding, of dihydroxyvitamin D analogs, in human keratinocytes)
IT Skin
(keratinocyte, differentiation and proliferation of human, dihydroxyvitamin D analogs effect on, structure in relation to)

IT 40013-87-4, 24,25-Dihydroxyvitamin D
RL: FORM (Formation, nonpreparative)
(formation of, as hydroxyvitamin D metabolite, by keratinocytes of humans, dihydroxyvitamin D analogs effect on)
IT 60133-18-8, 1,25-Dihydroxyergocalciferol 78782-99-7 91874-90-7
103335-39-3 **119290-65-2**
RL: BIOL (Biological study)
(hydroxyvitamin D metabolism by keratinocytes of humans response to)
IT 32222-06-3, 1,25-Dihydroxyvitamin D 72696-49-2 118694-43-2
124409-58-1
RL: BIOL (Biological study)
(keratinocytes of humans differentiation and proliferation response to, dihydroxyvitamin D receptors binding by, structure in relation to)
IT 21343-40-8, 25-Hydroxyvitamin D
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by keratinocytes of humans, dihydroxyvitamin D analogs effect on)
IT **119290-65-2**
RL: BIOL (Biological study)
(hydroxyvitamin D metabolism by keratinocytes of humans response to)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:517616 HCAPLUS
DN 119:117616
ED Entered STN: 18 Sep 1993
TI Vitamin D3 analogs
PA Daikin Industries, Ltd., Japan
SO U.S., 6 pp.
CODEN: USXXAM
DT Patent
LA English
IC C07J072-00
INCL 552653000
CC 32-7 (Steroids)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5200536	A	19930406	US 1992-832888	19920210 <--
	CA 2107471	AA	19930811	CA 1993-2107471	19930126 <--
	CA 2107471	C	20021029		
	WO 9316040	A1	19930819	WO 1993-JP88	19930126 <--
	W: CA, HU, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 579840	A1	19940126	EP 1993-902528	19930126 <--
	EP 579840	B1	19950809		
	R: BE, DE, FR, GB, IT				
	HU 65350	A2	19940502	HU 1993-2847	19930126 <--
	JP 07508501	T2	19950921	JP 1993-513939	19930126 <--
PRAI	US 1992-832888	A	19920210 <--		

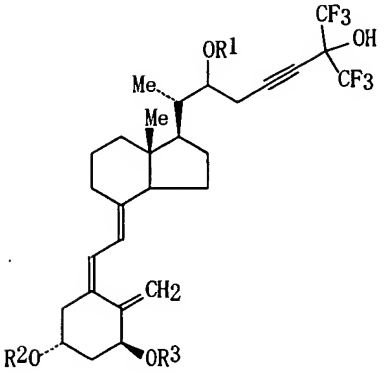
WO 1993-JP88 W 19930126 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5200536	IC	C07J072-00
	INCL	552653000
US 5200536	NCL	552/653.000 <--

OS MARPAT 119:117616

GI



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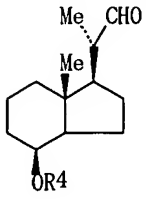


II

AB Fluorine-containing vitamin D analogs I (R1, R2, R3 are independently H or a hydroxy protecting group), having excellent pharmacol. activities, such as tumor cell differentiation-inducing activity, were prepared starting from hexahydroindanacetaldehyde II (R4 = Me3CSiMe2).

ST fluorine vitamin D analog

IT Neoplasm inhibitors
(fluorine-containing vitamin D3 analogs with cell differentiation-inducing activity)

IT 149219-61-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(Wittig reaction of, with protected (oxahexahydroindanyl)hexynol derivative)

IT 144100-39-0P 144177-07-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and Wittig reaction of, with protected [(methylenecyclohexylidene)ethyl]diphenylphosphine oxide)

IT 144100-36-7P 144177-04-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acetylation of)

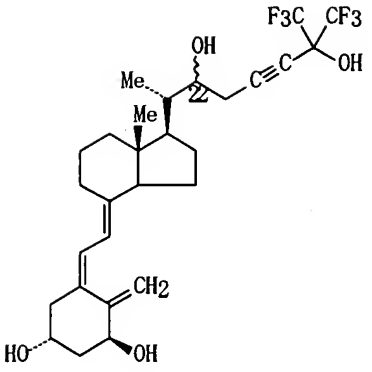
IT 144100-37-8P 144177-05-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deacetylation of)

IT **144100-33-4P** 144177-02-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and neoplasm-inhibiting activity of)

IT 144100-38-9P 144177-06-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and oxidation of, by pyridinium chlorochromate)

IT 104651-47-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with protected bromobis(trifluoromethyl)butynol)

GI



I

AB A convergent synthesis of the title compds. I, fluorinated analogs of the 1,25-dihydroxyvitamin D3, which modulates butyrate-induced differentiation of HT-29 human colonic carcinoma cells with very little effect of bone calcium mobilization is reported.

ST homovitamin D3 hexafluorotrihydroxy cell differentiation carcinoma; fluorotrihydroxyhomovitamin D3 prepn cell differentiation carcinoma; hydroxyvitamin D3 fluorinated analog

IT Neoplasm inhibitors
(fluorinated analogs of dihydroxyvitamin D3)

IT 684-16-2, Hexafluoroacetone
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling reaction of, with lithiated siloxypropyne)

IT 32222-06-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(fluorinated analogs of, preparation and anticancer activity of)

IT **144100-33-4P** 144177-02-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and anticancer and bone calcium mobilization activity of)

IT 144100-34-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling reaction of, with C/D-ring fragment)

IT 144100-39-0P 144177-07-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling reaction of, with N-ring fragment)

IT 104651-47-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling reaction of, with bromoalkylene derivative)

IT 144100-37-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of)

IT 144100-41-4P 144100-43-6P 144177-05-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and desilylation of)

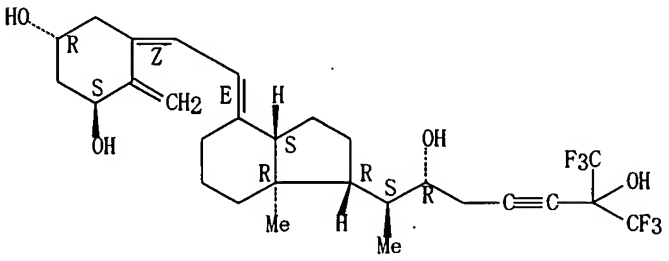
IT 144100-38-9P 144177-06-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and oxidation of)

IT 144177-03-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and ozonolysis of)

IT 144100-35-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and sequential lithiation and bromination of)

IT 144100-36-7P 144177-04-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and O-acetylation of)
IT 144100-40-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and O-deacylation of)
IT 144100-42-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and O-protection of, with methoxymethyl chloride)
IT 81522-68-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(sequential lithiation and coupling reaction of, with C/D-ring fragment)
IT 76782-82-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(sequential lithiation and coupling reaction of, with hexafluoroacetone)
IT 3188-13-4, Ethoxymethyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(O-protection by, of alkynol derivative)
IT 55812-82-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(O-silylation of)
IT **144100-33-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and anticancer and bone calcium mobilization activity of)
RN 144100-33-4 HCAPLUS
CN 1,3-Cyclohexanediol, 4-methylene-5-[(2E)-[(1R,3aS,7aR)-octahydro-7a-methyl-1-[(1S,2R)-7,7,7-trifluoro-2,6-dihydroxy-1-methyl-6-(trifluoromethyl)-4-heptynyl]-4H-inden-4-ylidene]ethylidene]-, (1R,3S,5Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:670839 HCAPLUS
DN 115:270839
ED Entered STN: 27 Dec 1991
TI Nongenomic actions of 1,25-dihydroxyvitamin D3 in rat osteosarcoma cells: structure-function studies using ligand analogs
AU Farach-Carson, Mary C.; Sergeev, Igor; Norman, Anthony W.
CS Dep. Biol. Chem., Univ. Texas, Houston, TX, 77030, USA
SO Endocrinology (**1991**), 129(4), 1876-84
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
CC 2-2 (Mammalian Hormones)
AB Osteoblast-like osteosarcoma cells (ROS 17/2.8) display a rapid transmembrane influx of extracellular Ca after stimulation by 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] this is mediated largely by the opening of voltage-gated Ca channels. These cells also constitutively express high nos. (>18,000/cell) of nuclear receptors for this seco-steroid hormone that are involved in the modulation of genomic activity in the osteoblast and in the up-regulation of transcription of

osteoblast-specific genes such as osteocalcin. The objective of this study was to determine the structural hierarchy of vitamin D3 analogs with regard to their efficacy as mol. transducers of the genomic and nongenomic pathways that are activated upon treatment of osteoblasts with 1,25-(OH)2D3. To test the structural features of the agonist required for initiation of these distinct pathways, a series of ligand analogs and naturally occurring metabolites of 1,25-(OH)2D3 were used that contain A-ring, D-ring, and side-chain modifications. The abilities of these analogs/metabolites to bind to nuclear receptors and stimulate transmembrane Ca influx were measured. Several analogs (25-hydroxy-16-ene-23-yne-D3 and 25-hydroxy-23-yne D3) stimulated Ca2+ channel opening, but bound only poorly to the 1,25-(OH)2D3 nuclear receptor. Conversely, other analogs (1,24-dihydroxy-22-ene-24-cyclopropyl D3 and 1,25-dihydroxy-16-ene-23-yne,26,27 F6-D3) bound very well to the nuclear receptor, but displayed little or no activity in opening Ca2+ channels. Pertussis toxin, which interferes with coupling of certain ligand-gated receptors to ion channels, failed to block the activation of Ca channels by 1,25-(OH)2D3 or active agonist analogs. The results indicate that there are likely to be distinct nuclear and plasma membrane-associated forms of the 1,25-(OH)2D3 receptor that are involved in genomic and nongenomic activation of osteoblast activity, resp. The membrane-associated receptors do not appear to be coupled to pertussis toxin-sensitive G-proteins.

ST dihydroxyvitamin D3 calcium transport osteoblast; calcitriol analog structure function

IT Receptors
RL: BIOL (Biological study)
(vitamin D3-related compds. binding by, of nucleus of osteoblast, mol. structure in relation to)

IT Cell nucleus
(vitamin D3-related compds. binding by, of osteoblast, mol. structure in relation to)

IT Osteoblast
(vitamin D3-related compds. effect on calcium transport and nuclear receptor binding by, mol. structure in relation to)

IT Biological transport
(channel-mediated, of calcium, by osteoblast, vitamin D3-related compds. effect on, mol. structure in relation to)

IT 19356-17-3 32222-06-3, 1,25-Dihydroxyvitamin D3 32222-06-3D, 1,25-Dihydroxyvitamin D3, analogs and metabolites 40013-87-4 41294-56-8 91874-90-7 103335-39-3 118694-43-2 **119290-65-2** 119290-66-3 124409-60-5 133910-08-4 137102-93-3 137102-94-4 137455-28-8 137493-88-0
RL: BIOL (Biological study)
(calcium transport response and nuclear receptor binding of, in osteoblast, mol. structure in relation to)

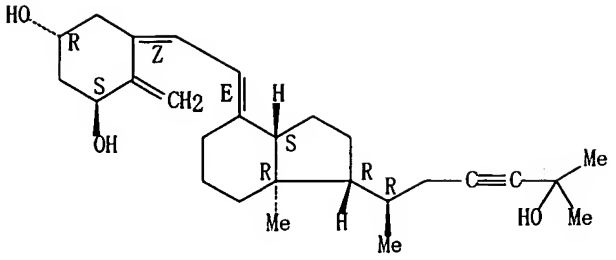
IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(channel-mediated transport of, by osteoblast, vitamin D3-related compds. effect on, mol. structure in relation to)

IT **119290-65-2**
RL: BIOL (Biological study)
(calcium transport response and nuclear receptor binding of, in osteoblast, mol. structure in relation to)

RN 119290-65-2 HCAPLUS

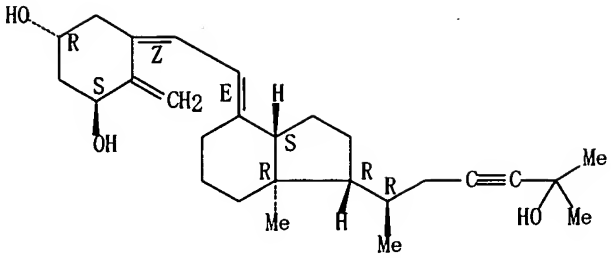
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:442695 HCAPLUS
DN 115:42695
ED Entered STN: 10 Aug 1991
TI Vitamin D analogs inhibit erythroid differentiation and induce monocytic differentiation of leukemic cells with the same relative potency
AU Kolla, Sarah S.; Moore, Dorothy C.; Studzinski, George P.
CS New Jersey Med. Sch., UMD, Newark, NJ, 07103, USA
SO Proceedings of the Society for Experimental Biology and Medicine (**1991**), 197(2), 214-17
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Myeloid leukemia cells of human and murine origin can be induced to differentiate into more mature forms which lose their neoplastic properties. The hormonal form of vitamin D is a powerful inducer of monocytic differentiation, but its therapeutic use is limited by hypercalcemia. It was recently reported that a novel derivative of vitamin D, 1,25-dihydroxy-16-ene-23-yne-vitamin D3, is an exceptionally potent inducer of monocytic differentiation, and prolongs survival of mice bearing leukemia cells. The authors show that this compound is also a most potent inhibitor of erythrodifferentiation. This finding has important implications for the control of hematopoiesis.
ST vitamin D erythroid differentiation monocyte; leukemia vitamin D analog; dihydroxyvitamin D3 leukemia hematopoiesis
IT Leukemia
(monocytic differentiation of, vitamin D analogs induction of)
IT Erythropoiesis
(vitamin D analogs inhibition of)
IT 1406-16-2D, Vitamin D, analogs 32222-06-3 83805-11-2 101558-90-1 104797-38-8 118694-43-2 **119290-65-2**
RL: BIOL (Biological study)
(erythroid differentiation and monocytic differentiation of leukemia cells response to)
IT **119290-65-2**
RL: BIOL (Biological study)
(erythroid differentiation and monocytic differentiation of leukemia cells response to)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

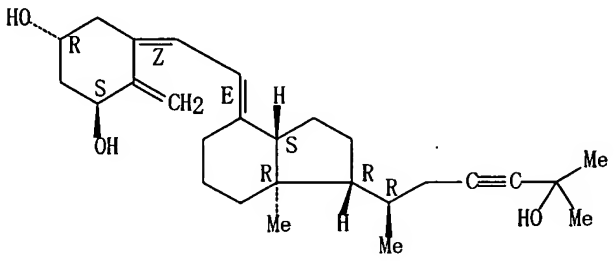
Absolute stereochemistry.
Double bond geometry as shown.



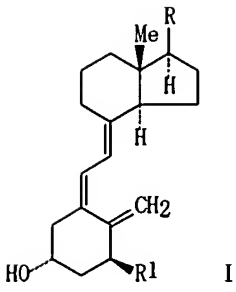
L21 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:526544 HCAPLUS
DN 111:126544
ED Entered STN: 14 Oct 1989
TI Novel vitamin D analogs that modulate leukemic cell growth and differentiation with little effect on either intestinal calcium absorption or bone calcium mobilization
AU Zhou, Jian Yuan; Norman, A. W.; Lubbert, M.; Collins, E. D.; Uskokovic, M. R.; Koeffler, H. P.
CS Dep. Med., UCLA, Los Angeles, CA, USA
SO Blood (**1989**), 74(1), 82-93
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 2
AB Induction of terminal differentiation of leukemic and preleukemic cells is a therapeutic approach to leukemia and preleukemia. 1α,25-Dihydroxyvitamin D3 [1,25(OH)2D3] the hormonally active form of vitamin D3 can induce differentiation and inhibit proliferation of leukemia cells, but concns. required to achieve these effects cause life-threatening hypercalcemia. Seven new analogs of 1,25(OH)2D3 were discovered to be either equivalent or more potent than 1,25(OH)2D3 as assessed by an inhibition of clonal proliferation of HL-60, EM-2, U937, and patients' myeloid leukemic cells and induction of differentiation of HL-60 promyelocytes. Furthermore, these analogs stimulated clonal growth of normal human myeloid stem cells. The most potent analog, 1,25-dihydroxy-16-ene-23-ynevitaminD3, was .apprx.4-fold more potent than 1,25(OH)2D3. This analog decreased clonal growth and expression of c-myc oncogene in HL-60 cells by 50% within 10 h of exposure. Effects on Ca2+ metabolism of these novel analogs in vivo was assessed by intestinal Ca2+ absorption (ICA) and bone Ca2+ mobilization (BCM). Each of the analogs mediated markedly less (10-200-fold) ICA and BCM as compared with 1,25(OH)2D3. To gain insight into the possible mechanism of action of these new analogs, receptor binding studies were done with 1,25(OH)2-16-ene-23-yne-D3 and showed that it competed only .apprx.60% as effectively as 1,25(OH)2D3 for 1,25(OH)2D3 receptors present in HL-60 cells and 98% as effectively as 1,25(OH)2D3 for receptors present in chick intestinal cells. In summary, 7 novel vitamin D analogs were discovered that are more potent than the physiol. 1,25(OH)2D3 as measured by a variety of hematopoietic assays. In contrast, these compds. appear to have the potential to be markedly less toxic (induction of hypercalcemia). These novel vitamin D compds. may be superior to 1,25(OH)2D3 in a number of clin. situations including leukemia/preleukemia; they will provide a tool to dissect the mechanism of action of vitamin D secosteroids in promoting cellular differentiation.
ST vitamin D analog leukemia differentiation; calcium metab vitamin D analog
IT Bone, metabolism
Intestine, metabolism
(calcium metabolism by, vitamin D analogs effect on)
IT Leukemia
(differentiation of human, vitamin D analogs effect on)
IT Receptors
RL: BIOL (Biological study)
(for dihydroxy vitamin D3, vitamin D analogs interaction with, in humans and laboratory animal cells, leukemia inhibition in relation to)
IT Neoplasm inhibitors

(leukemia, vitamin D analogs as, against human cells)
IT Gene and Genetic element, animal
RL: BIOL (Biological study)
(c-myc, expression of, vitamin D analogs effect on, in leukemia of humans)
IT 1406-16-2D, Vitamin D, analogs 32222-06-3, 1,25-Dihydroxy vitamin D3 86701-33-9 101558-90-1 103335-39-3 103420-55-9 104870-37-3 118694-43-2 **119290-65-2** 122619-92-5
RL: BIOL (Biological study)
(leukemia of humans growth and differentiation response to, calcium metabolism in laboratory animals in relation to)
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, vitamin D analogs effect on, in laboratory animals, human leukemia growth and differentiation response in relation to)
IT **119290-65-2**
RL: BIOL (Biological study)
(leukemia of humans growth and differentiation response to, calcium metabolism in laboratory animals in relation to)
RN 119290-65-2 HCAPLUS
CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1989:107718 HCAPLUS
DN 110:107718
ED Entered STN: 03 Apr 1989
TI An evaluation of analogs of 1,25-dihydroxyvitamin D3 on the inhibition of proliferation and induction of terminal differentiation in cultured human normal keratinocytes
AU Holick, M. F.; Uskokovic, M.; Persons, K.; Horst, R.; Baggiolini, E. G.; Truitt, G. A.
CS Sch. Med., Boston Univ., Boston, MA, USA
SO Proceedings of the Workshop on Vitamin D (**1988**), 7th(Vitam. D: Mol., Cell. Clin. Endocrinol.), 362-3
CODEN: PWVDDU; ISSN: 0721-7110
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 18
GI



I

AB The 1,25-dihydroxyvitamin D3 analogs (I, R = hydroxyalkyl side chain; R1 = H, OH) were tested for their ability to inhibit proliferation and induce differentiation of HL-60 cultured leukemia cells and cultured human keratinocytes, to affect Ca2+ metabolism in the intestine and bone of vitamin D-deficient rats, and to bind to the rat intestinal 1,25-dihydroxyvitamin D3 receptor. Ro 23-6474 analog inhibited cell proliferation and induced differentiation while having few effects on calcium metabolism Thus, this analog could be effective in the treatment of psoriasis.

ST psoriasis vitamin D3 analog keratinocyte; cell proliferation differentation vitamin D3 analog

IT Animal cell
(differentiation and proliferation of human, dihydroxyvitamin D3 analogs effect on)

IT Receptors
RL: BIOL (Biological study)
(for vitamin D, dihydroxyvitamin D3 analogs binding to, psoriasis treatment in relation to)

IT Psoriasis
(treatment of, with dihydroxyvitamin D3 analogs, proliferation and differentiation response in human cells in relation to)

IT 32222-06-3 32222-06-3D, 1,25-Dihydroxyvitamin D3, analogs 60133-18-8, Ro 17-6218 72696-49-2, Ro 22-9343 78782-99-7, Ro 21-5535/2 83805-11-2, Ro 23-34194 86677-62-5, Ro 23-0233 91874-90-7, Ro 23-6710 95783-08-7, Ro 23-6709 101558-90-1, Ro 23-4319 103420-55-9, Ro 23-6005 104418-75-9, Ro 23-6889 104797-38-8, Ro 23-6536 104870-37-3, Ro 23-6474 114906-52-4, Ro 21-5535/3 **119290-65-2**, Ro 23-7498 119290-66-3, Ro 23-9375
RL: BIOL (Biological study)
(cell proliferation and differentiation response to, calcium metabolism in, in humans and laboratory animals, psoriasis treatment in relation to)

IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, dihydroxyvitamin D3 analogs effect on, psoriasis treatment in relation to)

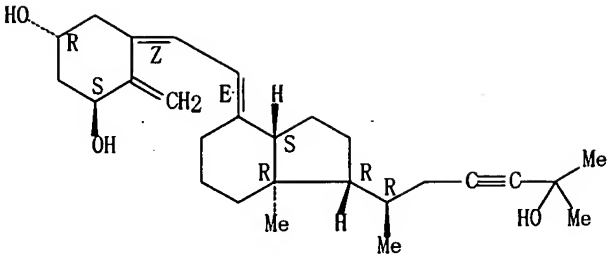
IT 1406-16-2, Vitamin D
RL: BIOL (Biological study)
(receptors for, dihydroxyvitamin D3 analogs binding to, psoriasis treatment in relation to)

IT **119290-65-2**, Ro 23-7498
RL: BIOL (Biological study)
(cell proliferation and differentiation response to, calcium metabolism in, in humans and laboratory animals, psoriasis treatment in relation to)

RN 119290-65-2 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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L23 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:273505** HCAPLUS
DN 139:358288
ED Entered STN: 09 Apr 2003
TI Combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents experimental autoimmune encephalomyelitis and preserves bone
AU Van Etten, E.; Branisteanu, D. D.; Overbergh, L.; Bouillon, R.; Verstuyf, A.; Mathieu, C.
CS Laboratory of Experimental Medicine and Endocrinology, Catholic University of Leuven, Louvain, 3000, Belg.
SO Bone (New York, NY, United States) (**2003**), 32(4), 397-404
CODEN: BONEDL; ISSN: 8756-3282
PB Elsevier Science Inc.
DT Journal
LA English
CC 1-7 (**Pharmacology**)
AB The vitamin D analog TX527 (19-nor-14,20-bis epi-23-yne-1,25(OH)2D3), decreased disease severity ($P < 0.001$) and postponed disease onset ($P < 0.0001$) in SJL mice in which exptl. autoimmune encephalomyelitis was induced. Levels of IFN-γ and IL-2 mRNA were decreased in spinal cord and spleen in the analog-treated mice, suggesting a Th1-targeted effect. Adding the bisphosphonate pamidronate did not affect analog-protective efficacy, but completely prevented TX527-induced acceleration of bone turnover and increased total bone mineral content as well as femoral mineral and calcium content ($P < 0.01$). Thus, Less calcemic analogs of 1,25-dihydroxyvitamin D3, in combination with bone sparing products such as bisphosphonates allow immune modulation in vivo without affecting bone.
ST immunomodulator dihydroxyvitamin D3 analog bisphosphonate exptl autoimmune encephalomyelitis bone; multiple sclerosis model immunomodulator TX527 bone sparing bisphosphonate
IT Multiple sclerosis
(animal model; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Immunosuppressants
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Interleukin 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression in spinal cord and spleen; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Interleukin 4
Osteocalcins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Autoimmune disease
(exptl. autoimmune encephalomyelitis; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

IT Encephalomyelitis
(exptl. autoimmune; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT T cell (lymphocyte)
(helper cell/inducer, TH1; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Spinal cord
Spleen
(interferon-γ and interleukin-2 expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Bone formation
(mineralization; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Bone
(resorption; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-, expression; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, expression in spinal cord and spleen; combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT 32222-06-3, 1,25-Dihydroxyvitamin D3 **163379-89-3**, TX527
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
IT 57248-88-1, Pamidronate disodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
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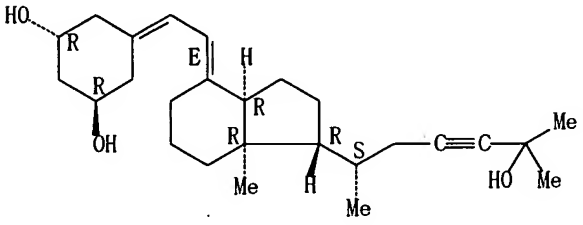
IT **163379-89-3**, TX527
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents exptl. autoimmune encephalomyelitis and preserves bone)

RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L23 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

AN **2002:467583** HCAPLUS

DN 137:261692

ED Entered STN: 23 Jun 2002

TI Treatment of autoimmune diabetes recurrence in non-obese diabetic mice by mouse interferon-β in combination with an analogue of 1α,25-dihydroxyvitamin-D3

AU Gysemans, C.; Van Etten, E.; Overbergh, L.; Verstuyf, A.; Waer, M.; Bouillon, R.; Mathieu, C.

CS Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven, Louvain, Belg.

SO Clinical and Experimental Immunology (**2002**), 128(2), 213-220
CODEN: CEXIAL; ISSN: 0009-9104

PB Blackwell Science Ltd.

DT Journal

LA English

CC 15-8 (Immunochemistry)
Section cross-reference(s): 1, 2

AB Autoimmune diabetes recurrence is in part responsible for islet graft destruction in type 1 diabetic individuals. The aim of the present study was to design treatment modalities able to prevent autoimmune diabetes recurrence after islet transplantation in spontaneously diabetic NOD mice. In order to avoid confusion between autoimmune diabetes recurrence and allograft rejection, the authors performed syngeneic islet transplantations in spontaneously diabetic NOD mice. Mice were treated with mouse interferon-β (IFN-β, 1+105 IU/day), a new 14-epi-1,25-(OH)2D3-analog (TX 527, 5 μg/kg/day) and cyclosporin A (CsA, 7.5 mg/kg/day) as single substances and in combinations. Treatment was stopped either 20 days (IFN-β and CsA) or 30 days (TX 527) after transplantation. Autoimmune diabetes recurred in 100% of control mice (MST 11 days). None of the mono-therapies significantly prolonged islet graft survival. Combining CsA with TX 527 maintained graft function in 67% of recipients as long as treatment was given (MST 31 days, vs. controls). Interestingly, 100% of the IFN-β plus TX 527-treated mice had normal blood glucose levels during treatment, and even had a more pronounced prolongation of graft survival (MST 62 days, vs. controls). Cytokine mRNA anal. of the grafts 6 days after transplantation revealed a significant decrease in IL-2, IFN-γ and IL-12 messages in both IFN-β plus TX 527- and CsA plus TX 527-treated mice, while only in

the IFN-β with TX 527 group were higher levels of IL-10 transcripts observed Therefore, the authors conclude that a combination of IFN-β and TX 527 delays autoimmune diabetes recurrence in islet grafts in spontaneously diabetic NOD mice.

ST autoimmune diabetes interferon dihydroxyvitamin D3 islet transplantation

IT Transplant and Transplantation
(allotransplant, islet; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Pancreatic islet of Langerhans
(allotransplant; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT T cell (lymphocyte)
(helper cell/inducer, TH1; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Autoimmune disease
(insulin-dependent diabetes mellitus; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Diabetes mellitus
(insulin-dependent; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interleukin 10
Interleukin 12
Interleukin 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Drug interactions
(synergistic; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interferons
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

IT 59865-13-3, Cyclosporin A **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

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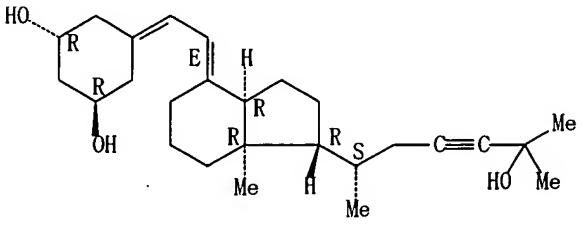
IT **163379-89-3**, TX 527
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interferon-β in combination with 1,25-dihydroxyvitamin analog for treatment of mouse autoimmune diabetes recurrence)

RN 163379-89-3 HCAPLUS

CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L23 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN

AN **2001:374037** HCAPLUS

DN 135:190779

ED Entered STN: 24 May 2001

TI Immunomodulatory properties of a 1,25(OH)2 vitamin D3 analog combined with IFNβ in an animal model of syngeneic islet transplantation

AU van Etten, E.; Gysemans, C.; Verstuyf, A.; Bouillon, R.; Mathieu, C.

CS Laboratory of Experimental Medicine and Endocrinology, Katholieke Universiteit Leuven, Louvain, Belg.

SO Transplantation Proceedings (**2001**), 33(3), 2319
CODEN: TRPPA8; ISSN: 0041-1345

PB Elsevier Science Inc.

DT Journal

LA English

CC 2-10 (Mammalian Hormones)
Section cross-reference(s): **1**, 15

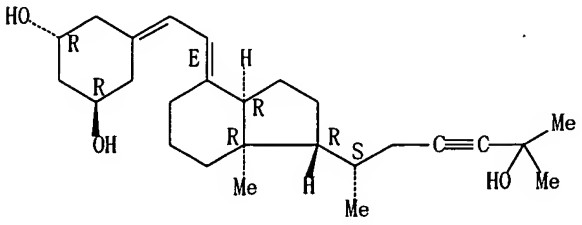
AB Immunomodulation obtained by combinations of TX527 (vitamin D3 analog), with interferon-β (IFNβ) and cyclosporin A (CyA) in syngeneic islet transplantation in spontaneously diabetic NOD mice was evaluated. All control mice showed disease recurrence within 2 wk after transplantation. The islet graft survival was not (TX527 and IFNβ) or only slightly (CyA) prolonged by monotherapies. Combination of TX527 with CyA and with IFNβ prolonged syngeneic graft survival.

ST TX527 interferon beta cyclosporin immunomodulation transplant

IT Immunomodulators
(immunomodulation by TX527 with cyclosporin A and IFNβ in

syngeneic islet transplantation)
IT Transplant and Transplantation
(pancreatic islet; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Drug interactions
(synergistic; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Pancreatic islet of Langerhans
(transplant; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
IT 59865-13-3, Cyclosporin A **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Van Etten, E; Transplantation 2000, V69, P1932 HCAPLUS
(2) Yong, W; Neurology 1998, V51, P682
IT **163379-89-3**, TX527
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunomodulation by TX527 with cyclosporin A and IFNβ in syngeneic islet transplantation)
RN 163379-89-3 HCAPLUS
CN 19-Nor-9,10-secocholesta-5,7-dien-23-yne-1,3,25-triol, (1α,3β,7E,14β,20S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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Section cross-reference(s): 2

AB The proliferative and differentiative effects of analogs of 1,25(OH)2 vitamin D3 [1,25(OH)2D3] were examined on a chronic myelogenous leukemia cell line, RWLeu-4, which is growth-inhibited and differentiates in response to 1,25(OH)2D3 (ED50 = 3-10 nM). Side-chain-fluorinated analogs were more potent (ED50 = 0.7-2 nM) while most of those with altered saturation of the D ring or side-chain carbon-carbon bonds were equally or less effective than 1,25(OH)2D3. However, the two analogs with either two addnl. double bonds or an extra double and triple bond in the D ring had greater antiproliferative activity [1,25(OH)2-16,23-diene D3 (ED50 = 2.7 nM) and 1,25(OH)2-16-ene-23-yne D3 (ED50 = 0.7 nM). Since the latter of these has been reported to be less potent at mobilizing calcium than 1,25(OH)2D3, it (or a similar compound) may be a candidate for clin. use as an antineoplastic agent.

ST hydroxyvitamin D3 analog myelogenous leukemia structure

IT Neoplasm inhibitors
(myelogenous leukemia, dihydroxy vitamin D3 analogs as, structure-activity relationship of)

IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, of dihydroxyvitamin D3 analogs, human chronic myelogenous leukemia proliferation and differentiation in relation to)

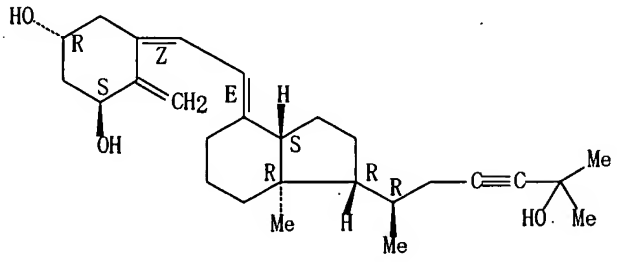
IT 32222-06-3 75227-86-0 78782-99-7 83805-11-2 91874-90-7 95783-08-7 101558-90-1 104418-76-0 118694-43-2 **119290-65-2** 119943-30-5 124409-57-0 124409-58-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, in human chronic myelogenous leukemia cell line)

IT **119290-65-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of, in human chronic myelogenous leukemia cell line)

RN 119290-65-2 HCAPLUS

CN 9,10-Secocholesta-5,7,10(19)-trien-23-yne-1,3,25-triol, (1α,3β,5Z,7E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L21 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1992:612777 HCAPLUS

DN 117:212777

ED Entered STN: 28 Nov 1992

TI Preparation of (22S)- and (22R)-24-Homo-26,26,26,27,27-hexafluoro-1,22,25-trihydroxy-24-yne-vitamin D3

AU Ohira, Yutaka; Taguchi, Takeo; Iseki, Katsuhiko; Kobayashi, Yoshiro

CS Tokyo Coll. Pharm., Hachioji, 192-03, Japan

SO Chemical & Pharmaceutical Bulletin (**1992**), 40(6), 1647-9
CODEN: CPBTAL; ISSN: 0009-2363

DT Journal

LA English

CC 32-7 (Steroids)
Section cross-reference(s): 1

OS CASREACT 117:212777